Falls as a result of being on Z-drugs for insomnia

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Key take home messages:

- Cognitive behaviour therapy is the recommended first line treatment for insomnia.
- Should Z-drugs be instead used for treatment of insomnia, treatment should be at the lowest dose and for the shortest period of time, typically 14 days.
- Recently published meta-analyses have consistently shown that Z-drug use is associated with an increased risk of falls-related injury with estimates ranging from OR 1.63 to RR 1.92.
- Zolpidem is associated with an increased risk of falls-related injury. Further studies are necessary to confirm if differential falls risk is associated with specific Z-drugs.
- Z-drug use appears to be associated with an excess of falls-related injury, even after correcting for comorbid insomnia.

Abstract
The widespread use of non-benzodiazepine receptor agonists ('Z-drugs') for the treatment of chronic insomnia persists, particularly in the elderly. Recently published meta-analyses have consistently shown that Z-drugs are associated with an increased risk of falls-related injury, which have a dose and time-dependent relationship similar to conventional benzodiazepines. Although insomnia itself can increase falls risk, there is some evidence to show that Z-drugs use results in an excess risk of falls independent of insomnia.

Although cognitive behavioural therapy is recommended as first-line therapy for insomnia, the widespread use of hypnotics persists, particularly in the elderly population. The non-benzodiazepine receptor agonists, known collectively as 'Z-Drugs', reduce sleep onset latency with a relatively preserved sleep architecture. However, the clinical effectiveness of the Z-drugs for the treatment of insomnia is modest at best. Polysomnography studies have shown that Z drugs reduce time to fall asleep by an average of 22 minutes; but do not improve other aspects of sleep such as number of awakenings, total sleep time, and subjective sleep quality.[1]

The Z-drugs have a shorter half-life (1-7 hours) compared to conventional benzodiazepines and have been promoted as safer hypnotics with less abuse potential. Early studies on zolpidem performed in mice up to 30 days and controlled trials in humans evaluating intermittent zolpidem use up to 10 weeks have suggested a lower likelihood of tolerance and physical dependence with repeated Z-drug use.[2,3] Although there is limited direct evidence of the risks of dependency in Z-drug use, evidence from studies investigating patient Z-drug use and prescribing patterns in the naturalistic setting suggest a similar adverse profile and propensity for addiction. In the elderly, addiction was observed in 51.8% of zolpidem users and 29.6% of zopliclone users, which was comparable to the addiction rate of 35-40% seen with bromazepam and lorazepam use.[4] In Norway, Z-drug prescriptions in the elderly renewed for repeat use comprised two-thirds of all Z-drug prescriptions, with more than half of prescriptions issued as large quantity prescriptions exceeding 50 tablets. Furthermore, Z-drug prescriptions have increased in parallel with a decrease in benzodiazepine prescribing in the past decade, particularly in the elderly population.[5] The American Geriatrics Society now recommends that Z-drugs not be prescribed beyond 90 days.[6] The NICE guidelines recommend all hypnotics are prescribed at the lowest dose and for the shortest period of time, typically fourteen days.[7] However, there is no data from randomised controlled trials to support fourteen days as a specific time period for Z-drug use.

Z drugs enhance the pharmacological action of GABA receptors in the CNS with a side effect profile similar to benzodiazepines; impairing cognition, gait and balance leading to an increased risk of falls. The elderly are particularly susceptible due to age-related alterations in the pharmacokinetics and pharmacodynamics. Accumulating medical co-morbidities and polypharmacy further increase the risks of falls, with sedative and anticholinergic medications particularly implicated. The English Longitudinal Study of Ageing showed that polypharmacy in the elderly with greater or equal than 10 drugs used was associated with a substantially 50% higher rate of falls over a two-year period. However, an increased falls risk was also seen at lower levels of polypharmacy with the use of just greater or equal to four drugs resulting in an increased falls risk by 21%.[8] Additional Z-drug use thus contributes to further falls risk in an already susceptible patient group. Single test doses of zopiclone administered to healthy elderly subjects result in dose-dependent impairment on postural stability and sway.[9] Zolpidem has been studied in the elderly in a small randomised placebo-control trial to assess balance and cognition during nocturnal awakening two hours after administration of a test dose and induced clinically significant impairments in balance even at the recommended reduced dose of 5mg.[10] Importantly, persistent impairments in balance were also observed 30

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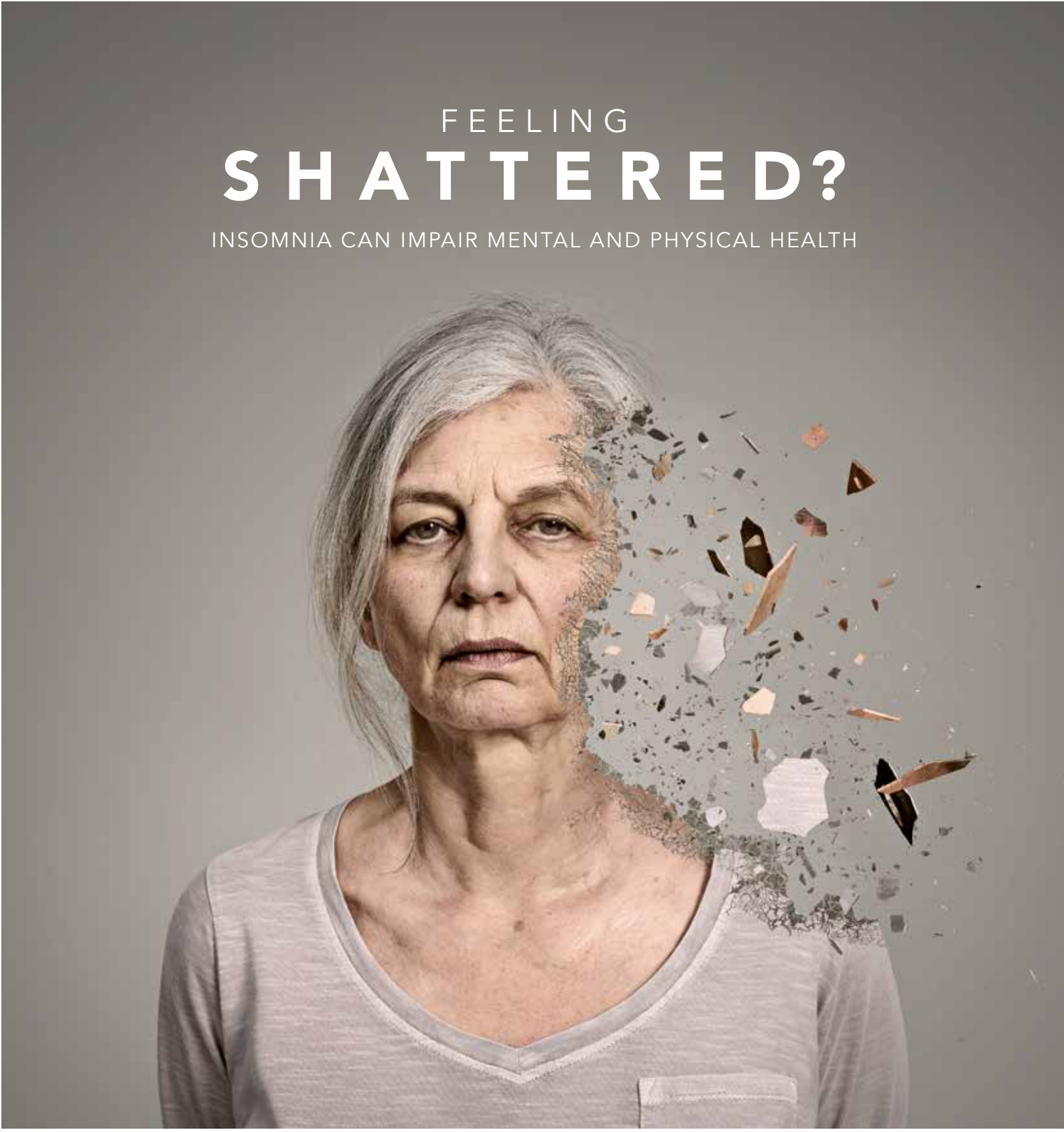

"For people over 55 years of age with persistent insomnia, consider treatment with a modified-release melatonin." - NICE CKS[1]

References and prescribing information can be found overleaf

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minutes after morning awakening. Tolerance to the cognitive and motor impairment related to Z-drugs may not occur even with chronic use.

The association between benzodiazepine use and increased risk of falls and fractures is well-established; with an often quoted meta-analysis suggesting that adverse outcomes related to benzodiazepine use outweighs the small benefits obtained: in this study, the number needed to treat for improved sleep was 13 as compared to the number needed to cause harm of only 6.[11] Z-drugs have been less well studied; however, there has been accumulating evidence that these drugs have a similar adverse profile to benzodiazepines.

The association of Z-drug use with serious falls with consequent hip fractures was first demonstrated in 2001 in a case-control study evaluating Medicare patients aged 65 and above undergoing surgery for hip fracture. Zolpidem was associated with the highest increased risk of hip fracture (AOR 1.95, 95% CI 1.09-3.51) compared to other medications studied including conventional benzodiazepines, antipsychotics and antidepressants which all increased fracture risk but less than zolpidem.[12]

There has since been accumulating evidence of the association between Z-drug use and falls-related fracture. Zolpidem has been the most studied drug with three recent meta-analyses all reporting an increased risk of falls-related injury of similar magnitude: OR 1.63, (95% CI, 1.42-1.87), RR 1.90, (95% CI 1.68 - 2.13) & RR of 1.92 (95% CI, 1.65, 2.24).[13-15] However, when falls were specifically examined as an outcome in a sub-analysis, Z drug use was not associated with a statistically increased falls risk although there was a trend to suggest an increased risk (OR 2.40, 95% CI 0.92, 6.27).[14]

To understand whether particular Z-drugs pose particular risks for falls: Yu studied the Taiwanese population and obtained an AOR of 1.24, 95% CI 1.38-1.89 with all Z-drug use with higher doses increasing risk;[16] a further study showed a differential effect of Z drugs on risk of falls with an increased risk of TBI (OR 1.87, 95% CI 1.56, 2.25) and hip fracture (OR 1.59, 95% CI 1.41- 1.79) with zolpidem but not with eszoplicone and zaleplon. However, the small number of individuals using zaleplon limited definitive conclusions.[17] Further studies are needed to confirm whether there are differential effects with regards to specific Z-drug use; however there looks to be a link between falls-related injury with Z drug use as a class, and in particular zolpidem.

One criticism of these studies is the confounding effect of insomnia and reduced sleep duration. Insomnia alone increases the risk of falls by impairing daytime function and increasing nocturnal awakenings.[18] One large study of elderly nursing home residents found that insomnia but not hypnotic use was associated with a greater risk of subsequent falls. The greatest risk was in those with untreated insomnia.[19] Therefore, treatment of insomnia using hypnotics in the elderly population could prevent falls.[18,20] However, without well conducted RCTs, this argument remains speculative with most evidence suggesting that Z drugs have a dose and time-dependent relationship with falls-related injuries. Treves attempted to correct for co-morbid insomnia by including studies with a control group diagnosed with insomnia. Importantly this still showed an increased, albeit attenuated, risk for fractures with Z drug use (OR 1.28, 95% CI 1.08, 1.53).[14] Longitudinal data from the Health and Retirement Study found that increasing insomnia symptoms predicted subsequent risk of falling in elderly subjects not using sleep medications. However, those prescribed sleep medications still had a consistently higher falls risk independent of insomnia symptoms compared to subjects not using sleep medications.[21]

Z-drugs may have their greatest risk when first prescribed. Donnelly showed that short term use of Z drugs (up to 14 days) was associated with the greatest risk of hip fractures (RR = 2.39, 95% CI, CI 1.74-3.29) compared to use beyond 30 days.[13] Z drugs are also associated with an excess risk of falls at night.[22] Thus, current prescribing guidelines that limit prescribing to short-term use of Z drugs may not avoid the adverse outcomes of increased falls.

In summary, recent studies have shown that Z-drugs are associated with an increased risk of falls-related injuries with a dose and time-dependent relationship similar to that observed with conventional benzodiazepines. Zolpidem has been particularly implicated. Prescribing guidelines to restrict chronicity of Z drug use, although well-intentioned, may not avoid the risk of falls-related injuries which tend to occur with initial rather than chronic use. A behavioural therapy should be first line treatment for insomnia where possible, particularly in the elderly population.

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