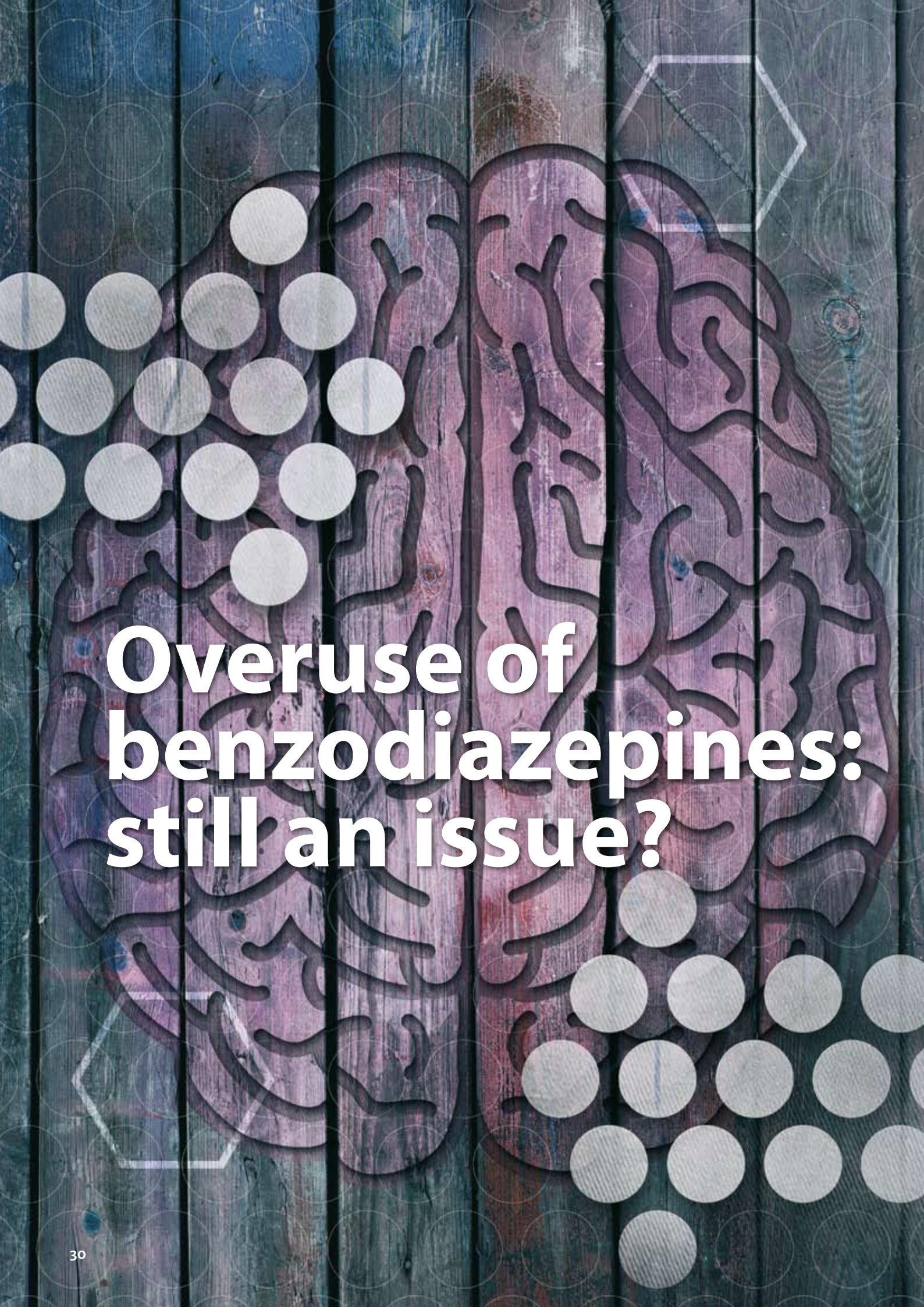

Overuse of benzodiazepines: still an issue?

Benzodiazepines may be considered as a short-term treatment for insomnia and anxiety; zopiclone, a benzodiazepine-like medicine, is indicated for the treatment of insomnia only. Benzodiazepines are also used in the treatment of epilepsy and as sedatives during medical procedures. Long-term use of these medicines for insomnia or anxiety is discouraged as they are associated with dependency, an increased risk of falls and dementia in elderly people, cognitive difficulties and an increased risk of motor vehicle accidents. Data from New Zealand show that patients are currently being prescribed large volumes of benzodiazepines and zopiclone.

Benzodiazepines and benzodiazepine-like hypnotics and anxiolytics are medicines which bring about a state of sedation, increased sleepiness, relaxation and impaired memory formation, depending on the drug and formulation used. Benzodiazepine-like hypnotics are often referred to as z-drugs due to the alliteration in their naming (zopiclone, zolpidem, zaleplon) and indication as hypnotics. Zopiclone is the only z-drug available in New Zealand. Benzodiazepines are Class C controlled drugs; zopiclone is not a controlled drug.

Benzodiazepines and zopiclone are used frequently in New Zealand

New Zealand pharmaceutical dispensing data shows that zopiclone is the most widely used funded hypnotic medicine. The number of patients dispensed zopiclone in 2013/14 was approximately equal to the total number of patients dispensed any benzodiazepine.[1] Zopiclone was the 14th highest volume medicine dispensed in New Zealand in 2013/14, with 120.2 dispensings (initial) per 1000 registered patients.[1] In comparison, there were 30.8 dispensings of lorazepam per 1000 registered patients in 2013/14 and 25.6 dispensings of diazepam; the two highest volume benzodiazepines dispensed.[1]

Benzodiazepine and zopiclone use in New Zealand is particularly prevalent in older people. A study on dispensing rates in 2011/2012 found that on average one in ten people aged 65 years and over, and one in five people aged 85 years and over, were dispensed a benzodiazepine in any quarter over this time period.[2] A recent assessment of medicine use in older people living in the community in New Zealand involved interviews with 316 participants aged 75 years and over. This study identified that 15% of participants were likely to be inappropriately using benzodiazepines and 9% inappropriately using zopiclone.[3] Inappropriate use included patients prescribed benzodiazepines long-term, at high-doses or using long-acting formulations, which should be avoided in elderly people.

Large volumes of benzodiazepines and zopiclone are being dispensed

Analysis of New Zealand dispensing data shows that there are many patients being prescribed large quantities of benzodiazepines and zopiclone (for any indication). It is uncertain to what extent these medicines are being used by the patients for whom they are prescribed, as opposed to being stockpiled, shared or even on-sold.

Zopiclone use in 2013

The recommended dosing regimen of zopiclone is up to one tablet (7.5 mg) at night, for a period of up to four weeks.[4] Therefore a patient could be dispensed up to 28 tablets for a single short course of use.

Among patients dispensed zopiclone in 2013:[5]

- 50% were dispensed 30 tablets or less
- 27% were dispensed between 30 and 150 tablets
- 23% were dispensed over 150 tablets (a total of 44,365 patients)

This suggests that half of patients were dispensed more zopiclone than is necessary for one treatment course in a one year period. While patients should only take zopiclone or benzodiazepines short-term for the treatment of insomnia, there are no clear clinical guidelines regarding an appropriate medicine-free interval before another short course is tried. Patients dispensed a large volume of tablets in one year may have taken several short courses of zopiclone, or may have been taking zopiclone on an as required ongoing basis throughout the year. Almost one-quarter of patients dispensed zopiclone received more than 150 tablets; this is the equivalent of (assuming the patient is taking one tablet, daily, as indicated):

- One tablet per day for at least five months if taken continuously
- At least three tablets per week taken over the entire year

There were 944 patients who received over 900 zopiclone tablets in 2013.[5]

Similar trends of dispensing are seen for triazolam and temazepam, benzodiazepines which are indicated for short-term use in the treatment of patients with insomnia (Table 1).

Prescribing points for benzodiazepines and zopiclone for insomnia or anxiety

Prescriptions for benzodiazepines or zopiclone should be written to take account of the risk of uncontrolled and escalating use, e.g. limited quantities with regular review. Prescribers should be vigilant for drug-seeking behaviour, such as early requests for repeat prescriptions.

For further information, see: "Prescription drug misuse: How to identify and manage drug seekers", BPJ 16 (Sep, 2008).

Prior to starting the medicine, patients should be given information about adverse effects, and understand that they are for short-term use only (if prescribed for insomnia or generalised anxiety) and educated about the importance of not becoming reliant on these medicines. Consider a treatment contract which covers treatment duration, dose parameters, outcome measures, adverse effects and review dates. This helps the patient to understand the expectations of their treatment and provides a safeguard for the clinician to avoid escalation of prescribing.

Prescription of benzodiazepines and zopiclone needs to be carefully considered as patients may perceive that the rapid symptom relief that is often gained when using these medicines outweighs any adverse effects and risks. Patients may be less willing to try other treatments that are not as instantly gratifying, such as SSRIs for anxiety or non-medical interventions for insomnia, but these are likely to be safer and more appropriate in the long-term.

For the treatment of anxiety

Benzodiazepines:

- Should not be routinely used to treat anxiety disorder unless there are specific reasons to believe they could offer short-term benefit[6]
- Are not recommended for the treatment of stress following a traumatic event[7]
- Are only recommended for short-term use

In addition to psychological support and counselling, pharmacological treatment options for anxiety include SSRIs, tricyclic antidepressants, buspirone and benzodiazepines. When considering prescribing benzodiazepines to a patient for short-term benefit, this should be balanced against the risk that even a brief prescription may encourage the patient to become reliant on a medicine to manage their anxiety. This may deter commitment to later psychological intervention.

For further information, see: "Generalised anxiety disorder in adults", BPJ 25 (Dec, 2009).

Table 1: The % (number) of patients dispensed zopiclone, temazepam or triazolam in 2013, by volume[4, 5]

	Zopiclone	Temazepam	Triazolam
Recommended volume of tablets for one course of treatment	Up to 28 tablets: 7.5 mg at night, for up to four weeks; 7.5 mg tablets	Up to 84 tablets: 10 – 30 mg at night, for up to four weeks; 10 mg tablets	Up to 20 tablets: 125 – 250 micrograms at night, for up to ten days; 125 or 250 microgram tablets
≤ 30 tablets	50.2% (97585)	51.5% (14130)	39.2% (10150)
31–90 tablets	19.5% (37868)	18.8% (5161)	20.2% (5223)
91–150 tablets	7.5% (14585)	6.5% (1790)	8.7% (2253)
151– 300 tablets	10.1% (19663)	7.8% (2131)	11.6% (3006)
> 300 tablets	12.7% (24702)	15.4% (4236)	20.4% (5273)

Table 2: Key prescribing information for benzodiazepines and zopiclone approved in New Zealand for the treatment of insomnia and anxiety.[4]

Key medical indication for use in primary care	Half life[a]	Recommended dose for healthy adults[b]
Insomnia		
Diazepam	long	5 – 15 mg at bedtime (insomnia)
Lorazepam	medium	1 – 2 mg at bedtime (insomnia)
Lormetazepam [c]	medium	0.5 – 1.5 mg at bedtime
Nitrazepam	long	5 – 10 mg at bedtime
Temazepam	short	10 – 30 mg half an hour before bedtime
Triazolam [c]	short	125 – 250 micrograms at bedtime
Zopiclone	short	3.75 – 7.5 mg at bedtime
Anxiety		
Alprazolam	short	0.5 – 4.5 mg daily
Diazepam	long	15 – 30 mg daily (anxiety)
Lorazepam	medium	1 – 4 mg (anxiety)
Oxazepam	short	30 – 120 mg daily

a Half-life definitions – short: less than 12 hours, medium: 12 – 24 hours, long: >24 hours. Half-life is likely to be longer in elderly or patients with renal impairment. The use of benzodiazepines with long half lives is not recommended in elderly patients.

b Elderly patients or those with co-morbidities such as renal impairment may require lower doses, often recommended as half the normal adult dose, see New Zealand Formulary for more details

c Partly subsidised; all other medicines in the table are fully subsidised

N.B. Clonazepam is not included in this table as its approved indication is for the treatment of epilepsy. However, in practice some clinicians use clonazepam to treat anxiety. It is a long-acting benzodiazepine; NZF does not list a dose for use in anxiety.

N.B. Benzodiazepines may be considered for reducing anxiety associated with breathlessness in patients during end-of-life care, if non-pharmacological treatments and morphine have not been effective.

For further information, see: "Managing breathlessness in palliative care", BPJ 47 (Oct, 2012).

For the treatment of insomnia

Benzodiazepines and zopiclone are not preferred treatment options, because:

- Cognitive-behavioural approaches (e.g. "sleep hygiene") have high levels of efficacy, are supported by a good evidence base, and achieve better outcomes in the long-term[8]
- Benzodiazepines are known to alter sleep architecture, with a reduced amount of time spent in slow wave sleep, reducing overall sleep quality compared to the equivalent duration of sleep achieved by cognitive-behavioural approaches[9]

If a benzodiazepine or zopiclone is being considered, because other interventions have been unsuccessful, a short-acting preparation should be chosen (Table 2) and prescribed at the lowest effective dose for a short duration; no more than four weeks, and preferably five to ten days.

For further information, see: "Managing insomnia", BPJ 14 (Jun, 2008).

Adverse effects of hypnotics can range from subtle to serious

Benzodiazepines and zopiclone can cause a range of adverse effects, which include:[10]

- Vertigo
- Muscle weakness
- Effects on cognition
- Dependency
- Increased risk of dementia and possible increased risk of Alzheimer's disease[11, 12]
- Sleep automatism (in the case of z-drugs), including food binging, and even driving, while still asleep or in a sleep-like state

These adverse effects can lead to clinical outcomes, such as an increased risk of falls, and increased risk of motor vehicle accidents.[10] There is some evidence that discontinuing the benzodiazepine or zopiclone reverses some of these effects, e.g. improvements in motor performance,[13] cognition,[13] and a reduction in dementia risk.[11]

Concomitant use of benzodiazepines or zopiclone with opioids or alcohol increases many risks, such as lack of judgement, sexual disinhibition, criminal activity and fatal overdose.

Elderly patients have reduced clearance of medicines from their body and are likely to need a lower dose of benzodiazepines or zopiclone to minimise adverse effects, such as half the normal adult dose. Benzodiazepines with a long half-life, e.g. diazepam and nitrazepam (Table 2), should be avoided due to an increased risk of falls with next-day drowsiness. Particular care needs to be taken with diazepam, which has both a long half-life and active metabolites.[10]

Withdrawing patients from long-term use of benzodiazepines or zopiclone

Strategies to encourage patients to stop a benzodiazepine or zopiclone should involve attempting to realign their perceptions of risks and benefits. Interventions which can be used in primary care to help change the way people perceive these medicines, and have been reported to increase rates of stopping hypnotic use, include:[14]

- Patient education with information brochures or booklets about discontinuing benzodiazepines, e.g.:
  - "Stopping benzodiazepines and Z-drugs" available from: **http://medical.cdn.patient.co.uk/pdf/4638.pdf**
  - "Benzodiazepines (tranquillisers and sleeping pills)", available from: **www.reconnexion.org.au/secure/downloadfile.asp?fileid=1015143**
- Regular follow-up letters to patients informing or reminding them of the risks of benzodiazepine use and the benefits of withdrawal
- Fortnightly consultations during withdrawal
- Psychological support: counselling or referral to psychological support services **substantially improves rates of discontinuation** over and above patient education or follow-up approaches

Withdrawal should be "slow but sure"

Rapid withdrawal of benzodiazepines is associated with an increased risk of seizures, therefore patients should be counselled against stopping their medicine abruptly.

Acute withdrawal can result in physiological and psychological effects, and a dose reduction strategy that aims to gradually wean patients off benzodiazepines and zopiclone is best practice. A gradual taper has been shown to improve the rate of successful discontinuation and avoid effects of withdrawal.[15] There is little evidence, however, of how frequently doses should be reduced, by how much, or the desired overall duration of weaning off these medicines.

Usual recommendations for benzodiazepine or zopiclone withdrawal are: [16]

- Dose reductions every one to two weeks, e.g. 10–15% of the initial dose depending on current dose and tablet strength/formulation
- Provide documentation of the treatment plan so that both patient and clinician can keep track of the planned reduction strategy. This is especially useful for patients who may be experiencing cognitive adverse effects.
- Monitor patient progress with frequent contact
- Be flexible – adjust reduction intervals according to how well a patient is tolerating the process. Some patients may manage a relatively quick reduction while others require a longer withdrawal process.
- If patients are experiencing difficulty, encourage them to remain on the lower dose they have achieved at that point, rather than increase the dose again. Recommence dose reduction when the patient feels able to resume.
- Patients should expect the possible occurrence of tremor, irritability, insomnia and anxiety during withdrawal stages, but these symptoms should alleviate once the withdrawal process is complete
- For patients with ongoing symptoms of anxiety

or depression, the use of alternative anxiolytics or antidepressants in addition to psychological support may be required

For patients who have difficulty withdrawing from benzodiazepines or zopiclone, such as those who find the process psychologically distressing or who develop strong withdrawal symptoms, consider discussing their situation with an addiction specialist or referring to addiction services; these patients may need more in-depth assistance than can be easily offered in a general practice setting.

Patients who have been taking benzodiazepines or zopiclone at high doses (e.g. > 20 mg diazepam per day) or for a long period of time (e.g. > ten years) are best discussed with an addiction specialist. These patients are likely to require a lengthy withdrawal period and more intensive psychological support and counselling.

N.B. Be aware that some patients may be taking very little, or any, of a seemingly large volume of benzodiazepines or zopiclone prescribed to them; drug-seeking rings commonly include older women who may raise less suspicion than younger males.

Patient support for benzodiazepine and hypnotic withdrawal

Patients may find benefit from interacting with others in a similar situation, or those who have prior experience with hypnotic addiction. This may be in the form of face-to-face patient-focused support groups or online support. Other support within the health care system or wider community is also available for patients with addiction to medicines.

New Zealand drug and addiction resources and services:

Drug help: **www.drughelp.org.nz**

Addictions treatment directory: **www.addictionshelp.org.nz/Services/Home**

New Zealand Drug Foundation: **www.nzdf.org.nz**

Alcohol drug help line: **0800 787 797**

Salvation Army addiction support: **0800 530 000**

Online information and support groups:

www.benzobuddies.org

www.benzosupport.org

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