Australian Government

Department of Health
Therapeutic Goods Administration

Our reference: Lex20760

Ms Bree Dyson
Coroner's Registrar
Coroners Court of Victoria
65 Kavanagh Street
Southbank VIC 3006

By email: cpuresponses@coronerscourt.vic.gov.au

Dear Ms Dyson

Subject: investigation into the death of Kelly E Hall

I refer to your letter dated 22 April 2016 addressed to Dr Larry Kelly of the Therapeutic Goods Administration (TGA), and the report of the Victorian Coroner of the same date and enclosed with your letter, regarding the above matter.

I also refer to my interim letter to you dated 22 June 2016 in which I advised that the TGA was considering the Coroner's recommendation that the TGA "*move all benzodiazepines into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons*" [most benzodiazepines are currently in schedule 4].

At the outset, please note that the TGA has treated the Coroner's report as a request to consider whether an application should be made to amend the Standard for the Uniform Scheduling of Medicines and Poisons (Poisons Standard), for example, at the initiative of the delegate of the Secretary under the *Therapeutic Goods Act 1989*. The TGA has not treated the Coroner's recommendation as an application to amend the Poisons Standard and, in any event, notes that the Coroner's recommendation does not under the legislation constitute an application to amend the Poisons Standard.

After careful consideration, the delegate was not satisfied that an application to amend the Poisons Standard to reschedule benzodiazepines from schedule 4 to schedule 8 is warranted at this point in time. In considering the matter, the delegate had regard to external independent advice and the fact that the delegate only recently considered an application to reschedule benzodiazepine derivatives from schedule 4 to schedule 8 or 9 of the Poisons Standard. I have elaborated on these matters below.

1. External Advice

As foreshadowed in my earlier letter, the TGA sought external independent advice on the data considered by the Coroner, and other data that may potentially support the

recommendation of the Coroner, to assist the TGA in deciding whether or not it would be appropriate to progress the Coroner's recommendation.

The TGA has now received the report of its external expert, a clinical pharmacologist. The TGA's external expert considered the current Coronial report and recommendation did not add significantly to the argument in favour of rescheduling all benzodiazepine drugs to Schedule 8. The report recommended that no further consideration be given to rescheduling those benzodiazepines in Schedule 4 to schedule 8 at this time.

The TGA's external expert report also considers the complex issue of benzodiazepine regulation more generally, including the possible consequences of providing more restrictive access regime, including the effect this would have on patients who need these drugs for bona fide medical reasons. Also, it considered whether a more restrictive access regime would result in the potential misuse of other substances and result in patients presenting with other medical issues. Overall, it considered that the results of a more restrictive access regime were inconclusive and based on experiences in other jurisdictions there may be positive and negative consequences.

A copy of the expert report (with the evaluator's name redacted for privacy reasons) is included at **ATTACHMENT A**.

2. Recent re-scheduling application

The delegate under the *Therapeutic Goods Act 1989*, who has responsibility for determining applications to amend the Poisons Standard, among other matters, recently considered an application to reschedule benzodiazepine derivatives (benzodiazepines not separately specified in the Schedules) from Schedule 4 to Schedule 8 or 9 of the Poisons Standard.

This was referred to the Advisory Committee on Medicines Scheduling (ACMS) which met in November 2015 and advised that:

- the following substances, not previously scheduled, be separately specified in Schedule 9: dicyclazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazepam, nifoxipam and meclonazepam; and
- the current scheduling of benzodiazepine derivative (class entry) otherwise remains appropriate.

The delegate taking into account the recommendations of the ACMS, made a final decision in June 2016 that the current scheduling of benzodiazepine derivatives (being a class entry) in Schedule 4 of the Poisons Standard remained appropriate. The reasons for the decision included that benzodiazepine derivatives capture both substances with legitimate medical uses and substances primarily used as drugs of abuse. Also, the delegate considered that while the longer term use of benzodiazepines may result in physical dependency the potential for abuse of the class overall would fit the criteria for a schedule 4 substance.

However, the delegate decided that the following benzodiazepines, not previously scheduled, be specified in schedule 9: dicyclazepam, pyrazolam, clonazolam, deschloroetizolam, flubromazepam, nifoxipam and meclonazepam on the basis they have no known therapeutic use in Australia and are contained in no registered products, but are available overseas. A link to the final decision can be accessed at the following link: https://www.tga.gov.au/book-page/21-benzodiazepine-derivatives.

While the ACMS meeting predates the Coroner's report, nonetheless, the issues raised by the Coroner's report were considered in the ACMS meeting in November 2015 and the subject of the delegate's decision in June 2016.

If you have any queries in relation to this matter, please do not hesitate to contact me on (02) 6232 8210 or via email at tony.gill@health.gov.au.

Yours sincerely

Dr Tony Gill
Acting Principal Medical Adviser
Therapeutic Goods Administration
Department of Health

Date 17 August 2016

ATTACHMENT A

Scheduling Evaluation Report

EVALUATION OF BENZODIAZEPINES RESCHEDULING PROPOSAL

Evaluation of the merit of a Recommendation from Victorian Coroner

[redacted]

22 July 2016

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1. EXECUTIVE SUMMARY

This evaluation has been undertaken in response to a recommendation in a report dated 22 April 2016 from Coroner Carlin of Victoria, following an investigation into the death of a patient from polydrug toxicity, that:

"In light of the evidence that the rescheduling of alprazolam has not reduced benzodiazepine contribution to overdose deaths in Victoria I recommend that within 12 months the Therapeutic Goods Administration move all benzodiazepines into Scheuld 8 of the Standard for the Uniform Scheduling of Medicines and Poisons."

In order to evaluate the merits of this recommendation, the Evaluator has considered the pharmacological aspects of the case that was the subject of the coronial report, carried out an updated literature review on the issue of polydrug abuse and the regulation of benzodiazepines, including published reports on the impact of the recent rescheduling alprazolam, and has considered the merits of the Coroner's recommendation on the background of this information. The regulation of benzodiazepines is a very controversial area, and there is no course of action that would be supported by all stakeholders.

The benzodiazepines (BDZs) are sedative-hypnotic drugs, commonly used to treat anxiety and insomnia, and also some cases of drug withdrawal, psychiatric conditions with acute agitation, and epilepsy. They have a very specific effect in the brain, and used alone are very safe drugs, with a remarkably low rate of serious outcomes even following very large overdoses. All BDZs have qualitatively similar pharmacological effects, although they differ in some quantitative aspects, particularly in relation to rate of onset and duration of action. They all share the property of losing their effect over time (pharmacological tolerance), so that higher doses are required to achieve the same effect, and the related property of inducing physiological and psychological dependence, so that an individual who has been taking a BDZ chronically is likely to develop withdrawal symptoms that include anxiety and insomnia if they attempt to cease taking the drug.

BDZs are very commonly abused by individuals who also abuse other drugs at the same time ("polydrug abuse"). When taken with alcohol or opioid drugs, either prescribed or illicit, BDZs may contribute to respiratory depression, which is commonly the cause of death following accidental overdose of this combination. The Coroner's Prevention Unit (CPU) investigated drug-related deaths in Victoria prior to the rescheduling of alprazolam, and found that prescription drugs were more commonly involved in drug-induced death than illicit drugs, and that the prescription drugs most commonly involved (often with either prescribed or illicit opioids) were diazepam and alprazolam (both BDZs). An update following the rescheduling of alprazolam to S8 has indicated a reduction in deaths in which alprazolam was a contributing factor, but no reduction in the overall impact of benzodiazepines as a group.

Published literature related to the rescheduling of alprazolam in 2014 indicates reduced use of alprazolam and an overall reduction in BDZ use by opioid dependent persons (Deacon et al 2016) and a reduction in both prescribing rates and calls to a state-based poisons centre related to alprazolam overdose (Schaffer et al 2016). The latter study showed increased switching to a different benzodiazepine, primarily diazepam and oxazepam. However, no unintended harms were noted in either report.

Several issues were involved in the polydrug abuse related to the death investigated by the Coroner. One set of issues related to inappropriate prescribing by two different GPs who did not coordinate their prescribing, chronic treatment with BDZs, and concomitant prescription of more than one BDZ to a patient who was on an opioid substitution program and had a long history of opioid dependence. The patient was also taking seven other drugs (non-BDZs) that would be expected to cause sedation. It is also noted that drug paraphernalia and remnants of white powder were found at the scene of death, suggesting the possibility of a relapse of heroin abuse. It would not be reasonable to conclude that the BDZs were the sole, or even primary, contributor to the death.

It is therefore RECOMMENDED that, given the lack of merit in the recommendation by the Coroner, no further consideration be given to rescheduling of all BDZs to Schedule 8 at this time.

2. PURPOSE OF APPLICATION

Background

This evaluation report is an assessment of the merits of a recommendation made in a report from a Victorian Coroner (Coroner Carlin; Court Reference: COR 2013 002123, dated 22 April 2016) on the death of a person (KEH) from combined drug toxicity in May 2013.

Based on data from the Coroners Prevention Unit (CPU) on Victorian drug overdose deaths for the period 2009-2015, the Coroner concluded that "most deaths each year (70% on average) were the result of combined drug toxicity rather than a single drug." Further, the Coroner commented that, based on the CPU data, "among pharmaceutical drugs, benzodiazepines were the most frequent contributing drug group to Victorian overdose deaths – and the benzodiazepine diazepam was the most frequent individual contributing drug."

The Coroner went on to opine that "there is clearly an urgent need to re-visit the question of benzodiazepine rescheduling, which in my view has still not been satisfactorily resolved." In 2012, Coroner Jamieson, also from Victoria, recommended that: "To reduce the harms and death associated with benzodiazepine use in Victoria, within 12 months the Therapeutic Good Administration of the Australian Government Department of Health and Ageing should move all benzodiazepines into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons." In response to this recommendation, the Advisory Committee on Medicines Scheduling (ACMS) decided to reschedule alprazolam to Schedule 8, because of its frequent misuse in combination with other drugs, and apparently reduced safety in overdose in comparison to the other drugs in the benzodiazepine (BDZ) class. Thus, alprazolam and flunitrazepam are now included in Schedule 8, while all other registered drugs in the BDZ class remain in Schedule 4.

Coroner Carlin notes that the preliminary evidence available to the CPU regarding the effect of the alprazolam rescheduling on Victorian overdose deaths indicates that there was a marked decrease in the annual frequency of overdose deaths in which alprazolam was involved. However, there was no overall decrease in the frequency of overdose deaths involving BDZs. These data contradict the published results of

Deacon et al (2016) reporting a reduction in overall BDZ usage in an opioid-dependent population, the group in which polydrug toxicity is most commonly seen.

Coroner Carlin concluded that "the rescheduling of only one benzodiazepine merely shifts the harm to other benzodiazepines" and recommended that:

"In light of the evidence that the rescheduling of alprazolam has not reduced benzodiazepine contribution to overdose deaths in Victoria I recommend that within 12 months the Therapeutic Goods Administration move all benzodiazepines into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons."

There is thus no formal application as would usually be submitted by a Sponsor, and in considering the recommendation, this Evaluator has read all of the material in the report of Coronial Findings and has also accessed the medical literature (referenced at the end of this report) to assess the merits of Coroner Carlin's proposal.

3. SUBSTANCE

Benzodiazepines (BDZs) are sedative-hypnotic drugs, commonly used to treat anxiety and insomnia. They have their effect by promoting the binding of the major inhibitory neurotransmitter gamma-aminobutyric acid (GABA) to its receptor on neurons within the central nervous system (CNS), thus enhancing the inhibitory effect of naturally occurring GABA (basic information on BDZs summarized in Charney et al 2006). BDZs in common use within Australia and available under Schedule 4 include clonazepam, diazepam, lorazepam, midazolam, nitrazepam, oxazepam, and temazepam. Flunitrazepam and alprazolam are scheduled as controlled drugs (S8), primarily for safety and public health reasons.

The pharmacological effects of BDZs are all qualitatively similar although they vary in some important quantitative respects, particularly related to their rate of onset and duration of action. Virtually all effects result from their actions on the CNS, and the most prominent are sedation, hypnosis (in the sense of induction of sleep), decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. An important property of all BDZs is their propensity to induce pharmacological tolerance, where, after more than a few weeks of continuous therapy, a progressive increase in dose is required to achieve the same effect. An associated property is the development of dependence, so that people who have been taking BDZs continuously for more than a few weeks develop withdrawal symptoms (anxiety, insomnia, dysphoria, tremor, irritability, sweating, unpleasant dreams and dizziness) if they stop taking them.

The therapeutic role of BDZs includes treatment of anxiety disorders, short-term insomnia (e.g. related to acute life events), management of alcohol withdrawal symptoms, anaesthetic premedication, short-term sedation in acute psychiatric disorders with agitation, and management of seizures. Long term use of BDZs is not recommended, except in rare cases of epilepsy unresponsive to other anticonvulsants.

Adverse effects of BDZs are related directly to their actions in the CNS, and include lightheadedness, lethargy, somnolence, motor incoordination, confusion, and anterograde amnesia. Unlike barbiturates, BDZs alone have little effect on respiratory drive although they do contribute to sedation. Overdoses of BDZs, even when the dose is very large, rarely cause any serious outcomes unless alcohol or another CNS depressant has been taken concomitantly. Deaths involving BDZs often also involve

alcohol, and true coma is uncommon in the absence of another CNS depressant (alcohol or another psychotropic drug, particularly opioids). Further information relating to the BDZs is provided below under 4.1.

4. EVALUATION

Background to Coroner's recommendations

The Coroner's report provided the following information, which is pertinent to the Coroner's recommendation and forms, in effect, the argument in favour of rescheduling of BDZs from Schedule 4 to Schedule 8.

The deceased person, who will be referred to in this report as KEH, was judged to have died from "mixed drug toxicity including methadone". The clinical details relevant to this evaluation are as follows:

- The medical history of KEH included the following:
    - Heroin and benzodiazepine addiction and alcohol abuse
    - Chronic back pain and sciatica, hepatitis C, morbid obesity
    - Anxiety, depression and borderline personality
- Medical treatment was provided by two separate general pracitioners (GPs), who became aware of each other but did not formally coordinate their care of KEH. Neither GP was fully aware of the prescriptions being provided by the other.
- Prescription history included:
    - GP1 obtained a permit from Drugs and Poisons Regulation to prescribe methadone as opioid replacement therapy; methadone treatment was interrupted from 1997 because of relapse in heroin use, but recommenced in 2000 and continued until the time of death.
    - GP1 was consulted by the patient two weeks before death, and prescribed her "usual" medications: methadone 45mg daily, diazepam 25mg daily, oxazepam 30-60mg nightly and zopiclone (a non-BDZ sedative-hypnotic) 7.5mg nightly
    - GP2 was first consulted in 2007, and 6 weeks before the death of the patient prescribed amitriptyline 50mg nightly (a tricyclic antidepressant) for depression, pregabalin 450mg daily, paracetamol + codeine combination (dose not provided but presumed to be combination tablets containing paracetamol 500mg + codeine 30mg) for pain, and zopiclone 15mg nightly.
    - Forensic evidence (see below) also indicated that the patient was taking duloxetine, a serotonin-uptake inhibiting antidepressant, which did not appear on the prescription list for either GP.
- KEH was last seen alive 16 hours before her body was discovered. Evidence obtained at the scene of death included a number of empty prescription medicine packets (including empty blister packs of diazepam, pregabalin, paracetamol and duloxetine and partially full blister packs and/or boxes of diazepam, pregabaline, duloxetine and amitriptyline) and related items,

including two empty methadone bottles, as well as drug paraphernalia and a zip lock bag containing remnants of white powder. No information is provided as to the identification of the nature of the white powder.

The autopsy findings relevant to this evaluation are as follows:

- Mild chronic ischaemic changes within the heart and features consistent with viral hepatitis
- Toxicological results indicating the presence of methadone (0.4mg/L) and its metabolite EDDP (0.05mg/L), amitriptyline (0.6mg/L) and its metabolite nortriptyline (0.4mg/L), pregabalin (15mg/L), duloxetine (0.37mg/L), diazepam (0.5mg/L) and its metabolite nordiazepam (0.8mg/L) and paracetamol (21mg/L). The time of sampling of blood specimens is not provided, but if the samples were obtained at the time of autopsy, which was done five days after death, it is possible that other substances might have been ingested and not been detected – an example would be heroin, which has a very short half-life measured in minutes, and its metabolite morphine, which has a short half-life of a few hours. Even if the sampling was done soon after discovery of the body, the drug concentrations in those samples are likely to have been much lower than they were at the time of death. If the sampling was delayed by several days, the drug concentrations of the medications that were detected would have been much lower than they were at the time of death.
- The cause of death was attributed to "mixed drug toxicity including methadone"; no comment is made in the Coronial report about the presence at the scene of the drug paraphernalia and white powder, which may have indicated a relapse of heroin addiction and concomitant use with the prescribed medication.

Coroner's recommendation

In relation to benzodiazepine scheduling specifically, the Coroner recommended that: "In light of the evidence that the rescheduling of alprazolam has not reduced benzodiazepine contribution to overdose deaths in Victoria I recommend that within 12 months the Therapeutic Goods Administration move all benzodiazepines into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons."

Comments on the application/recommendation from the Coroner

The following comments are intended to assess the pharmacological merit of the Coroner's recommendation, based on the Coroner's report, the circumstances of the patient KEH, and on a literature review carried out by the Evaluator.

There is no question that the prescribing of potentially sedating drugs to KEH was inappropriate, and that the coordination of care, particularly related to prescribing, between the two GPs involved was inadequate. In the few weeks before death, KEH had been prescribed a number of drugs with sedative effects, all of which can interact with each other to produce more severe sedation. The relevant drugs with sedative actions in this case include methadone and codeine (opioids), diazepam and oxazepam (BDZs), zopiclone (a non-BDZ sedative), amitriptyline (a tricyclic antidepressant), and pregabalin (an anticonvulsant and analgesic for neuropathic pain). In addition,

duloxetine, which was also ingested by the patient, can cause sedation. It would therefore be unreasonable to conclude that the major cause of sedation was the two BDZ drugs.

It could be argued that there was also the possibility of heroin use on the day of death. Heroin, as a rapidly-acting opioid that reaches the brain very quickly, would have contributed substantially to the risk of respiratory depression, particularly on a background of the seven sedating drugs that had been ingested. It is far from clear that the primary issue in this case was related to the prescription of benzodiazepines. There was no evidence that KEH had recently increased her dose of BDZ, and after chronic use for many years (the exact starting date is not provided), she would have been very tolerant to the effects of BDZs and they would have been unlikely to have contributed significantly to the severe sedation that is assumed to have occurred prior to death.

The major issue related to BDZs identified in this case, as well as in many other deaths that have been reported to be associated with polydrug abuse, appears to be primarily one of inappropriate, or even improper, prescribing, well outside the guidelines for use of benzodiazepines. Regulation of BDZs has been controversial for many years (Woods 1998), and remains so. Addressing the inappropriate prescribing of BDZ by issuing guidelines has not been found to be effective, given the plethora of guidelines available and the on-going rise in prescription rates (Kollen et al 2012). Clearly some some members of the medical profession prescribe sedating drugs, including but not limited to BDZs, inappropriately to patients at risk of misusing them. There is good evidence that the majority of people misusing benzodiazepines to a potentially dangerous degree are also users of other substances (Jones et al 2012).

The argument then is whether or not prescriber behaviour can or should be managed through regulatory means, and particularly drug scheduling.

The publications referred to earlier (Deacon et al 2016 and Schaffer et al 2016) indicate that the rescheduling of alprazolam in Feburary 2014 has had an impact on usage of that drug, and also that the overall use of BDZs amongst opioid-dependent persons has declined. This has not yet translated into a reduction in the representation of BDZs in the polydrug combinations that have caused death in Victoria, but the rescheduling is relatively recent and the effect may not yet be apparent in the CPU data.

It is important also to consider potential unintended consequences and disadvantages of the Coroner's recommendation. There are many legitimate indications for short-term use of short-acting BDZs for a few days, such as transient insomnia due to hospitalization or situational crises, or severe anxiety symptoms related to acute psychiatric disorders. Long-acting BDZs such as diazepam are commonly used short-term for the management of alcohol withdrawal symptoms or status epilepticus. Midazolam is commonly used as a short-acting sedative during invasive procedures or as an intravenous sedative in intensive care settings. It would be inappropriate to take any action that would restrict access for people who benefit from BDZs, but there are few legitimate indications that require prolonged use. For example, clonazepam and clobazam are used in some patients with refractory epilepsy as anticonvulsants. It would be important in any rescheduling decision to take these uses into account.

4.1 Considerations under section 52E of the *Therapeutics Goods Act 1989*

Evidence assessed against section 52E:

(a) the risks and benefits of the use of a substance

Used as monotherapy for a short period, the risks of using BDZs are low (see toxicity in part (c)). However, as they have significant potential for physical and psychological dependency, prolonged use can result in untoward effects, particularly an inability to cease taking the drug without precipitating a withdrawal syndrome. The benefits of use are related to the indication – there is potential for benefit for patients with short-term insomnia or anxiety related to a stressful life event or an acute psychiatric illness, for example, but after prolonged use the benefits of ongoing use are limited only to the prevention of withdrawal symptoms.

(b) the purposes for which a substance is to be used and the extent of use of a substance

In relation to this evaluation, the purposes for which the BDZs are used include the medical treatment of anxiety, insomnia, panic disorder, acute psychiatric conditions associated with severe agitation, and alcohol withdrawal.

(c) the toxicity and safety of a substance

BDZs are inherently very safe compounds in terms of their potential toxicity when used alone. In therapeutic doses their adverse effects are related directly to the effects of sedation (lightheadedness, increased reaction time, impaired mental and motor functions). In elderly people, prolonged use of BDZs is associated with an increased risk of falls, which is largest during prolonged use of long-acting BDZs (Sylvestre et al 2012). Alprazolam has the highest hazard ratio for fall-related injuries in the elderly, with medium and long-acting BDZs (clonazepam, lorazepam, bromazepam) also having higher risks than shorter-acting drugs (e.g, temazepam).

Even very large overdoses of BDZs alone generally result in prolonged sedation, with little risk of clinically problematic respiratory depression, although this may not be the case for alprazolam. In an Australian study, alprazolam overdose has been found to be associated with a higher rate of admission to intensive care units and a higher frequency of requirement for ventilation (Isbister et al 2004). However, when used in combination with opioids, BDZs in general appear to have an additive effect on the respiratory centre and combined overdoses are significantly more dangerous than overdoses with BDZs alone (Jones et al 2012).

(d) the dosage, formulation, labelling, packaging and presentation of a substance

This varies among the different BDZs available in Australia, and details are not relevant to this evaluation.

(e) the potential for abuse of a substance

BDZs have a high potential for misuse because they can cause euphoria and sedation, and have a high potential for psychological and physical dependence (Charney et al 2006). The euphoric effects have been shown to be additive to those of opioid drugs (summarized by Jones et al 2012). There is some evidence that the population of people dependent on BDZs falls into two different categories (Woods 1998). The larger group comprises people in the general population who receive BDZs

chronically at relatively low doses for insomnia or mild anxiety. These people are often elderly and have been taking BDZs for long enough to have developed pharmacological tolerance and physical dependence, such that the drug no longer has any effect but its absence would result in withdrawal symptoms of worsened insomnia and anxiety. Some argue that this situation should not be classified as "abuse" and is not particularly harmful to the patients concerned (Woods 1998). Others disagree with this, as there is evidence for an increased risk of falls (Sylvestre et al 2012) and cognitive impairment in elderly individuals taking BDZs chronically, although the causal links to cognitive decline have not been clearly established (Mura et al 2012).

The second group consists of the relatively small population of drug abusers, usually those who abuse multiple substances, including prescription drugs. For these people BDZs are used as secondary drugs of abuse, possibly for the control of symptoms of withdrawal from other abused substances such as opioids (Woods 1998) or in some cases to increase the subjective effects of the opioid or other sedative drug (Jones et al 2012). While the patient of interest to the Coroner fell into the second group, the greater number of people with physical and/or psychological dependence on BDZs is in the first group, and the impact of rescheduling may differ between the two. Specifically, the first group generally obtains their BDZs from legitimate sources and are therefore more likely to be affected than those in the second group, who may obtain their BDZs from various sources, both legitimate and illicit (unaffected by scheduling) and are at much greater risk of serious harm or death.

(f) any other matters considered necessary to protect public health

The dilemma of BDZ regulation, as outlined by Woods (1998), is the difficulty of avoiding undue risks of abuse without reducing the availability of drugs that may benefit people who need them. The potential consequences of more restrictive regulation of BDZs are illustrated by the experience in New York State in 1989, where a triplicate prescription was introduced for all BDZs, with one copy being retained by the State Government Department of Health for monitoring. There have been very varied reports of benefits and harms in response to this initiative. The number of prescriptions for BDZs declined by about 50%, but prescriptions for other, older sedative-hypnotics (including barbiturates, which are much more hazardous in overdose) increased (Weintraub et al 1993, Woods 1998). The prescription rate of clonazepam in patients with epilepsy declined slightly, and this was only partially offset by increases in the prescription of other anticonvulsants, raising the possibility of an unintended adverse consequence of undertreatment (Simoni-Sastila et al 2004). Nursing home residents were taken off BDZs but many were switched to other psychoactive drugs, including neuroleptics, chloral hydrate and sedating antihistamines, all of which are potentially more hazardous than the BDZs they replaced (Woods 1998). In Emergency Departments, there was a marked reduction in presentations with overdoses of BDZs, but an increase in presentations associated with frank withdrawal syndromes or relapse of anxiety disorders, and in overdoses of other sedative-hypnotics (Woods 1998), although the total number of overdoses from these classes was reduced. There was also a reduction in the deliberate overprescription of BDZs leading to illicit diversion following the introduction of the triplicate prescribing regulations (Wolf 1993). Overall, there were both positive and negative outcomes following this regulatory change.

5. CONCLUSIONS

This is a very controversial issue that raises strong opinions that vary depending on the perspective of the observer. The ACMS was faced in 2013 with a similar recommendation, and made a pragmatic decision to reschedule the most abused and arguably the most dangerous BDZ, alprazolam.

The case of interest in the current evaluation had ingested five other sedating drugs in addition to BDZs and had possibly also used an illicit opioid drug shortly before death. It is not warranted to single out BDZs as the primary contributor to death.

Careful assessment of the Coroner's recommendation, the clinical features of the case of interest, and the literature related to BDZ regulation, suggests that this recommendation to reschedule all BDZs to Schedule 8 is lacking in merit.

Recommendation

It is therefore RECOMMENDED that, given the lack of merit in the recommendation by the Coroner, no further consideration be given to rescheduling of all BDZs to Schedule 8 at this time.

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7. ATTACHMENTS

None.