IN THE CORONERS COURT
OF VICTORIA
AT MELBOURNE

Court Reference: COR 2011 3420

FINDING INTO DEATH WITHOUT INQUEST

Form 38 Rule 60(2)
*Section 67 of the **Coroners Act 2008***

I, AUDREY JAMIESON, Coroner having investigated the death of JOHN RAYMOND GILBETT

without holding an inquest:
find that the identity of the deceased was JOHN RAYMOND GILBETT
born on 19 December 1956
and the death occurred on 11 September 2011
at 1 Birch Court, Kinglake West, 3757

from:

1 (a) HANGING[1]

Pursuant to Section 67(2) of the **Coroners Act 2008**, I make these findings with respect to the following circumstances:

1. Mr John Raymond Gilbett was 54 years of age at the time of his death. He had a son and a daughter and was self-employed with a small gardening and lawn mowing service.

2. Mr Gilbett was found deceased by his ex-wife Mera Gilbett in his bedroom at the Kinglake West home they shared, at approximately 12.00 pm on 11 September 2011. Mera Gilbett had last seen him alive at 10.30pm on the previous evening, when he went to his bedroom. At some time in the intervening 14 hours, John Gilbett used a rope to hang himself from his cupboard door; and what appeared to be a 'suicide note' was located in his bedroom. Emergency Services attended but were unable to render medical assistance to Mr Gilbett as it

[1] Death in hanging is the result of compression of the arteries and veins supplying and draining the head and neck, compression of the large airway, pressure on the carotid sinuses, or, as is often the case, a combination of all of the above.

was apparent that he had been deceased for some time. Attending police officers found several medications including varenicline[2] in Mr Gilbett's bedroom.

INVESTIGATION

3. Dr Michael Burke, Senior Forensic Pathologist at the Victorian Institute of Forensic Medicine (VIFM) performed an external examination upon the body of Mr Gilbett, reviewed a post mortem CT scan and reviewed the Victoria Police Report of Death, Form 83.

4. Toxicological analysis of blood retrieved post mortem identified the presence of morphine,[3] carbamazepine[4] and delta-9 tetrahydrocannabinol.[5] Varenicline was not detected, however at the time, the VIFM was not able to test for it.[6] Dr Burke ascribed the cause of Mr Gilbett's death to hanging.

5. The circumstances of Mr Gilbett's death have been the subject of investigation by Victoria Police. Police obtained statements from Mrs Mera Gilbett, General Practitioner (GP) Dr Kee Wong, GP Dr John Deady and an attending Paramedic.

6. Mrs Gilbett stated that Mr Gilbett reported feeling unwell and appeared restless and agitated after commencing Champix (varenicline) approximately two weeks prior to his death.

CPU REVIEW

7. The Coroners Prevention Unit (CPU)[7] reviewed the circumstances of Mr Gilbett's death on behalf of the Coroner. The CPU specifically looked at evidence regarding the association

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[2] Varenicline is a medication used to treat nicotine dependence and assist patients to cease smoking. It is sold under the trademark name, Champix.

[3] Morphine is a narcotic analgesic used to treat moderate to severe pain.

[4] Carbamazepine is an anti-convulsant used in the treatment of epilepsy, some types of neuralgia and schizophrenia. Only trace amounts of this substance was detected.

[5] Marijuana is the collective term for the dried leaves of the plant Cannabis or an extract of the plant. It is often referred to as "grass". Delta-9-tetrahydrocannabinol (THC) is one of the main psychoactive ingredients of Cannabis. A THC blood concentration of 9ng/mL was detected. The presence of THC in blood at a concentration in excess of 5ng/mL strongly suggests recent use of cannabis (within a few hours).

[6] In an email to the Court dated 24 October 2011, VIFM Medical Liaison Nurse Natalie Morgan stated that "Friday 21/10/11 I spoke with head of toxicology Dimitri Gerostamoulos who told me the toxicology department are unable to test for Champix (varenicline)".

[7] The Coroners Prevention Unit (CPU) was established in 2008 to strengthen the prevention role of the coroner. The unit assists the coroner with research in matters related to public health and safety and in relation to the formulation of prevention recommendations, as well as assisting in monitoring and evaluating the effectiveness of the

between varenicline and suicidality and the extant clinical prescribing guidelines for varenicline.

8. The CPU considered:

    a. the Coronial brief;

    b. Medicare Australia patient history report of Medicare benefits recorded for Mr Gilbett in the period 11 September 2010 to 11 September 2011;

    c. Pharmaceutical Benefits Scheme (PBS) patient summary of PBS benefits recorded for Mr Gilbett in the period 11 September 2010 to 11 September 2011; and

    d. Epping Plaza Medical and Dental Centre medical recording (which include a copy of Plenty Valley Medical Centre medical records).

Medical History

9. According to Mera Gilbett, her ex-husband was physically healthy and had no history of mental illness up until 30 April 2001, when he sustained significant injuries in a motor vehicle accident on the Melba Highway, including a head injury. In addition to ongoing chronic pain, the accident also had a lasting impact on his mental health. In Mera Gilbett's statement dated 12 September 2011, she explained that Mr Gilbett became "nearly psychotic" after the accident as well as moody and aggressive, and required continuous treatment for this:

> Since that accident John has been on medication. He was on Tegretol and Seroquel and also pain medication being MS Contin. [...] Since the accident he has been emotionally up and down but the medication kept him stable.[8]

10. The available medical records go back to 4 September 2003, and are therefore unable to confirm that Mr Gilbett was physically and mentally well prior to 30 April 2001. However, it is clear that from 4 September 2003 through to his death, Mr Gilbett suffered a number of chronic conditions.

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recommendations. The CPU comprises a team with training in medicine, nursing, law, public health and the social sciences.

[8] Tegretol is a brand name of carbamazepine, a mood-stabilising drug. Seroquel is a brand name of the atypical antipsychotie quetiapine. MS Contin is a brand name for a controlled-release formulation of opioid analgesic morphine.

11. From September 2003 until October 2007, Mr Gilbett attended GP Dr Harry Kwiatek at the Plenty Valley Medical Centre in Mill Park. His attendances were regular (usually between two and four times per month), but there are indications in Dr Kwiatek's medical records that he was not John Gilbett's main treating GP. For example, in a patient medical history note dated 11 July 2007, Dr Kwiatek wrote:

> abscess r forearm from rose thorn regular doctor prescribing antibiotic she is treating dr eileen macdonald

12. The mention of "dr eileen macdonald" is probably Dr Ileene MacDonald, a GP based in Diamond Creek, whose medical records are not among the material available for the purpose of my investigation. In another note dated 24 January 2007, Dr Kwiatek wrote "own doctor looking into low", which appears to be an oblique reference to another doctor treating Mr Gilbett's low mood.

13. It is apparent from the available material that Dr Kwiatek might best be described as Mr Gilbett's pain and addiction doctor, which is a common practice in Victoria, where doctors qualified to provide opioid replacement therapy will often only treat drug dependence and leave all other aspects of medical care to other doctors. This is supported by a review of Dr Kwiatek's medical records from the Plenty Valley Medical Centre, which essentially contain nothing about Mr Gilbett's medical history or treatments other than his pain and addiction issues.

14. Mr Gilbett presented to Dr Kwiatek in September 2003 with back pain, and was addicted to opioids including morphine and heroin. At various times over the next four years, Dr Kwiatek prescribed methadone and buprenorphine for both analgesia and to treat his opioid dependence, as well as oxycodone, tramadol and morphine for analgesia. Correspondence in the medical records identify pain and addiction experts including Dr Benny Monheit, Dr Bruce Kinloch, Dr Michael McDonough and Dr Tobie Sacks, who were regularly involved in reviewing Mr Gilbett and providing treatment advice to Dr Kwiatek.

15. Mr Gilbett's medical records suggests that over the period in which Dr Kwiatek provided treatment at the Plenty Valley Medical Centre, Mr Gilbett presented as a challenging patient. He continually reported that his medications were lost or stolen, took medications in larger than prescribed quantities, and came up with repeated reasons why drug dispensing restrictions (put in place to prevent him gaining access to too many opioids at once) should be

relaxed. During a consultation in February 2007, he even reported that mice had eaten his methadone tablets, and requested a further script. He also engaged in doctor shopping, as indicated in a letter from Dr Monheit to Dr Kwiatek dated 20 September 2007:

> We discussed the fact that he [...] got morphine tablets from five different doctors (although a total of only five scripts) between January and March 2007. John puts this down to an increasing need for pain relief. I find it is hard to work out how much of John's behaviour is due to opiate tolerance, or drug abuse.

16. In addition to the opioids, in July 2005 Dr Kwiatek commenced John Gilbett on carbamazepine (brand name Tegretol), a mood stabiliser also used to treat neuropathic pain. Dr Kwiatek did not indicate in his notes why he prescribed carbamazepine. In May 2006, Dr Kwiatek commenced John Gilbett on the antidepressant citalopram (brand name Cipramil), again without making any notation as to why this occurred.

17. It is possible that Dr Kwiatek prescribed carbamazepine and citalopram at the advice of Psychiatrist Dr Tobie L Sacks. In a letter to Dr Kwiatek dated 20 February 2006, Dr Sack states:

> Although there are still some problems arising out of the head injury [John Gilbett] sustained in April 2001, his mood and behaviour have stabilised with carbamazepine and citalopram.

18. As this letter predates Dr Kwiatek prescribing citalopram, it is possible that Dr Sacks may have been treating Mr Gilbett and prescribing drugs to him in parallel with Dr Kwiatek.

19. In October 2007, Mr Gilbett ceased receiving treatment for his chronic pain and drug addiction at the Plenty Valley Medical Centre, and commenced treatment at the Epping Plaza Medical and Dental Centre. He however remained under the care of Dr Kwiatek, suggesting his move to the new medical centre might have been related to Dr Kwiatek moving.

20. Mr Gilbett's medical history shows that Dr Kwiatek continued treating him at the Epping Plaza Medical and Dental Centre through to approximately October 2009, when the bulk of his treatment was taken over by Dr Jack Deady and Dr Kee Wong. Just prior to this handover, on 9 September 2009, Dr Kwiatek recommenced Mr Gilbett on citalopram (it is not clear when the citalopram was ceased). His note indicated: "feeling depressed no home wife asked to leave depressed counselled".

21. The patient medical history and other documents show that the main features of Mr Gilbett's presentations (chronic pain, opioid dependence, doctor shopping and drug seeking) remained consistent through to his death while under the treatment of Drs Deady and Wong. These doctors also continued to prescribe citalopram through to mid-2010, when according to Dr Deady's statement dated 15 September 2011:

> He had stopped his Cipramil medication around July 2010 and he found that he was doing okay off them and I reserved the opportunity to go back on antidepressant medication if it was needed.

22. Neither Dr Deady nor Dr Wong indicated in their notes that mental ill health was a major issue for Mr Gilbett.

23. In the PBS Patient Summary for John Gilbett for the period 11 September 2010 to 11 September 2011, there are several prescribers listed from clinics other than the Epping Plaza Medical and Dental Centre, including Dr Vijaya Balasundarum at the Morriset Medical Centre in New South Wales, who prescribed the antipsychotic quetiapine on several occasions. However, given the scope of my investigation, information from practitioners where there is no evidence of varenicline prescribing was not pursued.

Varenicline

24. Varenicline is a medication used to treat nicotine dependence and to assist patients to cease smoking. It is described as a nicotinic receptor partial agonist, because it binds to nicotinic receptors in the brain and stimulates them to release dopamine, thus mimicking the effect of nicotine inhaled in tobacco smoke. It also has antagonistic properties, blocking the ability of nicotine to bind at receptor sites, thus reducing its effect. The combination of these two effects is believed to be the basis of varenicline's efficacy as a smoking cessation aid.[9] Strong evidence from numerous studies shows that varenicline is more effective than either a placebo or nicotine replacement therapy at assisting people to cease smoking.[10]

25. Varenicline is marketed in Australia by Pfizer under the brand name Champix. In February 2007, the Therapeutic Goods Administration (TGA) approved it for use as "an aid for

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[9] Lam S, Patel P, "Varenicline: A selective A4B2 nicotinic acetylcholine receptor partial agonist approved for smoking cessation", *Cardiology in Review*, vol 15, no 3, May-June 2007, p.155.

[10] Cahill K, et al, "Pharmacological interventions for smoking cessation: an overview and network meta-analysis (Review)", *The Cochrane Collaboration*, 2013, p.3.

smoking cessation in adults over the age of 18 years", whereupon it was listed under Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) as a prescription-only medication.[11] It was also listed on the Pharmaceutical Benefits Scheme (PBS) in January 2008 as an authority required medication, meaning that a PBS benefit can only be claimed if it is dispensed consistently with PBS clinical and treatment criteria.[12]

How varenicline is prescribed and taken

26. Varenicline is available in two different packages, the 'commencement' and the 'continuation' packages. The commencement package comprises 11 tablets of 0.5mg varenicline and 42 tablets of 1mg varenicline, and its authority-required use is for the commencement of a short-term (12 to 24 weeks) course of treatment. Its authority required clinical criteria are:

    a. the treatment must be as an aid to achieving abstinence from smoking; and

    b. the treatment must be the sole PBS-subsidised therapy for this condition; and

    c. the patient must have indicated they are ready to cease smoking.[13]

27. The varenicline commencement authority-required treatment criteria are:

    Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time the Authority application is requested. Details of the support and counselling program must be documented in the patient's medical records at the time treatment is

[11] Therapeutic Goods Administration, "Public summary: 124944 Champix varenicline (as tartrate) 1.0mg tablet bottle", *Australian Register of Therapeutic Goods*, updated 31 March 2014.

[12] The Pharmaceutical Benefits Scheme (PBS) subsidises the cost of prescription medications for eligible Australian residents. The name of the subsidy paid by the PBS for a prescribed medication is the "PBS benefit". Most medications are subsidised without restriction. This means the PBS benefit is paid regardless of the therapeutic purpose for which the medication is prescribed. Some medications are subject to a restricted benefit, meaning the PBS benefit is only paid if the medication is prescribed for therapeutic uses specified in the PBS Schedule of Pharmaceutical Benefits. An authority required benefit is a type of restricted benefit where the prescriber must obtain approval from the Commonwealth Department of Human Services to issue the prescription for the medication. If no approval has been obtained for the authority required benefit, a PBS benefit cannot be claimed. However, the medication can still be prescribed and dispensed so long as the patient pays the full cost. For a detailed explanation see Commonwealth Department of Health and Ageing, "Prescribing Medicines: Information for PBS Prescribers", <http://www.pbs.gov.au/info/healthpro/explanatory-notes/section1/Section_1_2_Explanatory_ Notes>, accessed 16 May 2013.

[13] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 7 October 2014.

initiated. Clinical review is recommended within 2 to 3 weeks of the initial prescription being requested.[14]

28. The continuation package comprises 56 tablets of 1mg varenicline, and its authority-required use is for continuation of a short-term (12 to 24 weeks) course of treatment. Its authority required clinical criteria are:

    a. the treatment must be as an aid to achieving abstinence from smoking; and

    b. the treatment must be the sole PBS-subsidised therapy for this condition; and

    c. the patient must have previously been issued with an authority prescription for this drug during this current course of treatment.[15]

29. The varenicline continuation authority-required treatment criteria are:

    Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program.[16]

30. The general process for taking varenicline is described in the Champix Consumer Medical Information produced by Pfizer. In brief, the patient should choose a date at which time the patient intends to cease smoking. The patient commences taking varenicline between one and five weeks before the chosen quit date, using the commencement package. The commencement course of tablets is used as follows:

    a. first three days, take one 0.5mg tablet daily (this gets the body used to the drug);

    b. days four to seven, take one 0.5mg tablet at morning and another at night; and

    c. weeks two to four, take one 1mg tablet at morning and another at night.

31. Taken in this way, the commencement package should last for the first month of treatment. The patient then switches to the continuation package (56 tablets of 1mg varenicline), taking

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[14] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 7 October 2014.

[15] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 7 October 2014.

[16] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 7 October 2014.

one tablet at morning and another at night. The aim is that the patient should have stopped smoking after taking varenicline for 12 weeks. At this stage, the patient might cease varenicline, however the doctor might recommend a further 12 weeks of treatment (at the continuation dosage) to increase the chances of long-term smoking cessation. If the patient is still smoking at 12 weeks, the treatment course can be recommenced.[17]

How varenicline was prescribed and dispensed to Mr Gilbett

32. The available material suggests that Mr Gilbett was prescribed varenicline on two occasions. On the first occasion, 17 August 2009, Dr Kwiatek prescribed the varenicline while treating Mr Gilbett at the Plenty Valley Medical Centre. His entry in the patient medical history reads:

> Counselling abstinence willingness. Seeing psychiatrist relating to tca no meds counselling antidepressants apparently lft raised psychiatrist will follow up no etoh or hepc in past

33. The only part of this entry that appears to relate to the varenicline is the first three words - "counselling abstinence willingness", which presumably indicate that Dr Kwiatek counselled Mr Gilbett regarding his willingness to quit smoking and the importance of abstaining from tobacco. The bulk of the entry appears to indicate that Mr Gilbett was seeing a Psychiatrist relating to a tricyclic antidepressant ('tca') and there was some issue regarding his liver functioning test ('lft') but he was not consuming alcohol ('etoh') and did not suffer hepatitis C ('hepc').

34. The accompanying prescription notation in the patient medical history for the above entry indicated "1 - Champix (combination pack)". I assume this meant that Mr Gilbett was prescribed a commencement package containing a combination of 11 tablets of 0.5mg varenicline and 42 tablets of 1mg varenicline. As no PBS patient summary for Mr Gilbett that covers August 2009 was obtained, I am unable to confirm whether the varenicline was dispensed on this occasion. As there are no subsequent notes in the patient medical history about the varenicline, I am similarly unable to establish whether Mr Gilbett completed the course of treatment and whether the treatment was successful.

[17] Pfizer Australia, "Champix varenicline tartrate: Consumer Medical Information", January 2014, pp.2-3.

35. The second occasion on which Mr Gilbett was prescribed varenicline occurred on 22 February 2011. Dr Deady prescribed the varenicline while treating Mr Gilbett at the Epping Plaza Medical and Dental Centre. His entry in the patient medical history reads:

> Wants to QUIT many options disc
> Try Champ disc
> Long disc also re meds etc

36. The accompanying prescription notation in the patient medical history for the above entry indicated "1 - Champix (combination pack)". The PBS patient summary for Mr Gilbett confirmed that on 22 February 2011, the varenicline was dispensed to him through the PBS at Whittlesea Pharmacy. The PBS entry reads:

> PBS item code 09128K. Varenicline box containing 11 tablets 0.5mg (as titrate) & 1 4 tablets 1mg

37. The Whittlesea Pharmacy were contacted on 9 October 2014 to confirm the amount of varenicline dispensed. The duty Pharmacist confirmed that that a standard commencement package of 11 tablets 0.5mg and 42 tablets 1mg varenicline was dispensed. It therefore appears that the PBS entry was probably erroneous regarding the amount of 1mg tablets dispensed.

38. The subsequent entry by Dr Deady regarding varenicline on 24 February 2011 reads: "ok č Champ", which is interpreted as "ok with Champix". In Dr Deady's Coronial Brief statement dated 15 September 2011, he explained the overall varenicline prescribing as follows:

> On February this year [...] he had asked about stopping smoking and we discussed various different options. He settled to try on Champix and I duly gave him a prescription to commence on this medication to help with quitting smoking. He was doing quite well on this but stopped on his own accord around March, as he had an altercation with his wife to whom he was married for about 24 years and she asked him to leave the house.

39. As indicated in Mera Gilbett's statement, Mr Gilbett recommenced on varenicline approximately two weeks prior to his death. The recommencement is documented in Dr Deady's patient medical history entry dated 31 August 2011: "Started on Champix 1/52 ago doing ok on it". It is also mentioned in a subsequent entry dated 5 September 2011: "crook??

Champix blurred head abdo sore diarr N. etc try half Champ". Dr Deady clarifies these notes in his statement as follows:

> On 31 August 2011 he informed me that he was wanting to quit smoking and he had restarted himself on the Champix about the week previously and told me he was doing ok on it at that stage. [...] I next saw him on 5 September 2011, unfortunately also the last time and he had been feeling a little bit blurry in the head and some diarrhoea. We thought it may have been either some gastroenteritis or due to a side effect of the Champix and I suggested he cut to half the usual dose of Champix. This may have been because he had started on the dose he had stopped with, instead of starting on a lower dose.

40. There is no indication in the Epping Plaza Medical and Dental Centre patient medical history or Coronial Brief statements, that Dr Deady or anybody else provided another varenicline script to John Gilbett at this time. The PBS patient summary similarly does not show any varenicline dispensing. Coroner's Investigator Senior Constable (S/C) Cameron Caine was contacted to find out whether the Champix package photographed at the death location had a legible prescription label on it. S/C Caine indicated that he had taken the package as evidence but they had no labels, and I was therefore unable to confirm whether or not Mr Gilbett had obtained varenicline more recently than 22 February 2011.

41. Absent evidence to the contrary, it appears that when Mr Gilbett recommenced taking varenicline in late August 2011, he probably continued with the varenicline that had been dispensed on 22 February 2011, and which he had ceased taking (according to Dr Deady's statement) in March 2011.

42. Mr Gilbett attended the Epping Plaza Medical and Dental Centre on two final occasions prior to his death, being 7 September 2011 and 9 September 2011. On both occasions he was seen by Dr Wong. There is no mention of varenicline in Dr Wong's patient medical history entries for these dates, but in his Coronial Brief statement dated 13 September 2011 he wrote:

> He said [on 7 September 2011] he was still smoking a few cigarettes, but was feeling better since he had halved the dose of Champix 1mg. He said he had set his quit date as 14 September 2011.

43. Dr Wong further noted that Mr Gilbett "seemed to be his usual self" on these last two attendances.

Co-occurrence of varenicline recommencement and Mr Gilbett's suicide

44. In Mera Gilbett's statement she noted a change in Mr Gilbett's mood and demeanour in the two weeks leading up to his death, which coincided with his recommencing varenicline. She wrote:

> About two weeks ago John started taking Champix to give up smoking. John began to take these and stated that he started to feel ill near the start of last week. On Saturday John spoke to me. John asked, "Is this what I am usually like, is this what I was like just after the accident? It shouldn't be like me."
>
> John was nearly psychotic after the accident and very moody and aggressive after the accident. John was starting to think he was going back to that. John felt nothing inside and distressed the way he was behaving and feeling. John was scared.
>
> I really noticed a change in John on Friday 9 September. His whole demeanour just changed. For the whole night John was irritable and restless. When John went out I was concerned that he wouldn't come back, I thought he was going to hurt himself because he went out into the bush.
>
> On Saturday I asked him what was wrong last night. John seemed better. He informed me he was alright. As the day went on John started to go downhill again. John said to me later in the afternoon, "It has to be the Champix, it's fucking with my head. I feel like I did after the accident". I informed John that he had been good for some time on the medication he was taking but had changed since taking the Champix one week ago.

45. Ambulance Paramedic Ronald McLeod, who attended at the Kinglake West home soon after Mera Gilbett found MrGilbett deceased, wrote in his Coronial Brief statement that:

> [Mera Gilbett] informed me that Mr John Gilbett's behaviour had changed over the last couple of weeks after he was prescribed Champix from his doctor. Mr John Gilbett's wife told me her husband had had dramatic mood swings after he had been prescribed Champix.

46. Similarly, Coroner's Investigator S/C Caine noted that when he attended the Kinglake West home, Mera Gilbett told him that John Gilbett "had started to take the drug Champix to give up smoking" and "was becoming very moody".

Varenicline and suicidality

47. Medical practitioners, public health experts and others have expressed concern that taking varenicline might be associated with suicidal thoughts and behaviour.

Evidence from post-market surveillance programs

48. Many international health systems run post-market surveillance (PMS) programs to which doctors, patients and drug companies are requested (and in some cases required) to report possible adverse events associated with approved pharmaceutical drugs. The adverse event reports are collated and analysed to identify any potential issues with drugs that were not identified during pre-approval clinical trials, and to alert patients and clinicians.

49. PMS program data is where potential associations between varenicline and suicidality were first identified; and this data remains the strongest evidence to date of a potential link.

i. United States of America (USA) alerts

50. In the USA, the Food and Drug Administration (FDA, an agency of the US Department of Health and Human Services) is responsible for approving pharmaceutical drugs. Its main functions are explained as follows:

> We evaluate new drugs for safety and effectiveness before they can be sold. Our evaluation, called a review, ensures that the drugs we approve meet our tough standards for safety, effectiveness and quality. Once drugs are on the market, we monitor them for problems.[18]

51. The FDA runs a PMS program called MedWatch, to which US healthcare providers, consumers and others can report a broad range of adverse events and medication errors that they suspect might be connected with pharmaceutical drugs. As a result of MedWatch data, the FDA has issued several alerts regarding varenicline as follows:

    a. on 20 November 2007, the FDA issued an Early Communication about reports of suicidal thoughts and aggressive behaviour among patients being treated with varenicline for smoking cessation;

[18] Food and Drug Administration Centre for Drug Evaluation and Research, *Centre for Drug Evaluation and Research Update: Improving Public Health Through Human Drugs*, 2007, p.7.

b. on 16 May 2008, the FDA announced "it appears increasingly likely that there is an association between [varenicline] and serious neuropsychiatric symptoms". Prescribing information was updated to alert patients, their families and treating practitioners about suicidal thoughts and actions;

c. on 1 July 2009, the FDA introduced a new label warning that people who experience "any serious and unusual changes in mood or behaviour" or "feel like hurting themselves" while taking varenicline should immediately contact a health care professional;

d. on 24 October 2011, the FDA reiterated the risk of serious events such as "changes in behaviour, hostility, agitation, depressed mood, and suicidal thoughts or actions" when using varenicline.[19]

ii. Australian alerts

52. The TGA's Advisory Committee on the Safety of Medicines (ACSOM, formerly the Adverse Drug Reactions Advisory Committee) runs a PMS program encompassing all medicines listed on the Australian Register of Therapeutic Goods (ARTG). Patients, health professionals, manufacturers and suppliers of pharmaceutical drugs are encouraged to report the following:

> What to report? You don't need to be certain, just suspicious.
>
> The TGA encourages the reporting of all suspected adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of:
>
> a. all suspected reactions to new medicines;
>
> b. all suspected medicines interactions; and
>
> c. suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.[20]

[19] Accessed via US Food and Drug Administration, "Postmarket Drug Safety Information for Patients and Providers", 9 August 2014, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm>, accessed 10 October 2014.

[20] This standard wording inviting reports of suspected adverse reactions is published on the TGA website and on the back page of publications such as *Australian Prescriber*.

53. The ACSOM regularly publishes alerts and notifications about particular drugs based on the reports received through the PMS program. Its alerts regarding varenicline have included:

    a. in December 2008, the TGA indicated it has received 339 adverse reaction reports regarding varenicline. Most reports identified psychiatric symptoms "including depression, aggression, agitation, abnormal dreams, insomnia, hallucination and anger", as well as suicidal ideation or behaviour. The TGA warned, "it appears increasingly likely with accumulating experience that there is an association between varenicline and serious neuropsychiatric events".[21]

    b. on 2 August 2010, a TGA update indicated that "psychiatric symptoms, including suicidal behaviour, continue to be reported with varenicline". Specifically, as at May 2010, the TGA had received reports of "206 suicide-related events in people taking varenicline, including 15 completed suicides".[22]

iii, Alerts in other countries

54. The Medicines and Healthcare Products Regulatory Agency (MHRA) runs the United Kingdom's (UK) PMS program, collecting reports about suspected side effects of medicines and vaccines, and issuing safety warnings and alerts about pharmaceutical drugs. In July 2008, the MHRA issued its first drug safety advice on varenicline, which had been approved for use in the UK in December 2006. The MHRA noted that it had received 129 reports of suicidal thoughts or behaviour associated with the use of varenicline, and warned patients and treating doctors about this.[23]

55. MedSafe is New Zealand's PMS program. Varenicline was approved for use in New Zealand in April 2007. In May 2009, an interim prescriber update on varenicline notifications to the MedSafe program described 22 reports of depression with onset while taking varenicline, including three patients who reported suicidal ideation. In response, a warning regarding suicidal ideation and changes in behaviour and mood was added to the packaging for varenicline dispensed in New Zealand.

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[21] Adverse Drug Reactions Advisory Committee, "Varenicline: the Australian experience so far", *Australian Adverse Drug Reactions Bulletin*, vol 27, no 6, December 2008, p.22.

[22] Elijah J, "Varenicline (Champix): an update", *Australian Prescriber*, vol 33. no 4, August 2010, p.120.

[23] Medicines and Healthcare Products Regulatory Agency, "Varenicline: suicidal thoughts and behaviour", *Drug Safety Update*, vol 1, no 12, July 2008, p.2.

56. In May 2013 the final MedSafe report on Varenicline was published, confirming that most adverse events associated with varenicline in New Zealand were behavioural: "unusual behaviour or thinking, agitation or depressed mood, suicidal thoughts or suicidal behaviour".[24]

iv. Interpreting PMS data

57. As the FDA acknowledges, there are a number of limitations with PMS data on pharmaceutical drugs:

> First, there is no certainty that the reported event (adverse event or medication error) was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS (FDA Adverse Event Reporting System) data cannot be used to calculate the incidence of an adverse event or medication error in the US population.[25]

58. Accepting these limitations (which apply not only to the FDA but to all PMS programs), PMS data is still widely acknowledged as a source of early warnings about potential issues with particular drugs, which can then be investigated more thoroughly through other studies.

Evidence from published research

59. Potential links between varenicline and suicidality have been explored in a wide range of published research. The following is a summary of some of the major themes and findings in the literature:

    a. attempts to examine whether varenicline causes suicidality are confounded by the robust finding that current smokers are at increased risk of suicide compared to the

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[24] http://www.medsafe.govt.nz/hot/papersreports/vareniclineimmp.asp.

25 Food and Drug Administration, "FDA Adverse Event Reporting System (FAERS) (formerly AERS)", 9 October 2012, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Surveillance/AdverseDrugEffects/default.htm>, accessed 19 June 2013. On this point see also Gibbons RD, Mann JJ, "Strategies for Quantifying the Relationship between Medications and Suicidal Behaviour What has been Learned?", Drug Safety, vol 34, no 5, pp.379-381.

general population, and that smoking cessation is associated with depression and therefore potentially with increased suicide risk;[26]

b. some studies of health outcomes among patients prescribed varenicline for smoking cessation have not found any evidence to suggest that varenicline is associated with a greater risk of self-harm than other smoking cessation products.[27] However other studies have reported increased risk of suicidality, self-harming behaviour and/or depression among varenicline users than either users of other smoking cessation drugs or the broader population;[28]

c. the literature includes several case reports of individuals who either developed suicidal ideation or who suicided after commencing on varenicline, some of whom had no previous history of mental illness or suicidality;[29]

d. several studies have been conducted on the safety and efficacy of varenicline for smoking cessation among those who suffer mental illness, usually comparing outcomes with a control group who do not suffer mental illness. Most studies have found that varenicline does not exacerbate mental illness or lead to worse outcomes than in patients without mental illness;[30] and

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[26] For a discussion see Hughes J, "Smoking and suicide: a brief overview", *Drug and Alcohol Dependence*, no 98, 2008, p.170; Mineur YS, Picciotto MR, "Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis", *Trends in Pharmacological Sciences*, vol 31, no 12, December 2010, p.580.

[27] Gunnell D, et al, "Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database", *British Medical Journal*, vol. 339, 2009, b3805; Gibbons RD, Mann JJ, "Varenicline, Smoking Cessation, and Neuropsychiatric Adverse Events", *American Journal of Psychiatry*, vol 170, no 12, December 2013, p.1464; Thomas KH, et al, "Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study", *British Medical Journal*, vol 347, 11 October 2013.

[28] Moore TJ, et al, "Suicidal Behavior and Depression in Smoking Cessation Treatments", *Public Library of Science One*, vol. 6, no 11, November 2011, p.1; Cowan CM, et al, "Use of the Patient Health Questionnaire-2 to Predict Suicidal Ideations in Patients Taking Varenicline", *The American Journal on Addictions*, vol 21, July-August 2012, p.358.

[29] Kintz P, et al, "Smoking Cessation with Varenicline: A Suicidal Fatality", *Journal of Analytical Toxicology*, vol 33, March 2009, p.118; Stove CP, et al, "Fatality following a suicidal overdose with varenicline", *International Journal of Legal Medicine*, vol 127, 2013, p.85.

[30] Stapleton JA, et al, "Varenicline in the routine treatment of tobacco dependence: a pre–post comparison with nicotine replacement therapy and an evaluation in those with mental illness", *Addiction*, no 103, 2007, pp.152-153; McClure JB, et al, "Mood, Side-effects and Smoking Outcomes Among Persons With and Without Probable Lifetime Depression Taking Varenicline", *Journal of General Internal Medicine*, vol 24, no 5, 2009, pp.565-566; Anthenelli RM, et al, "Effects of Varenicline on Smoking Cessation in Adults With Stably Treated Current or Past Major Depression", *Annals of Internal Medicine*, vol 159, no 6, September 2013, p.390;

e. there have been recent accusations that Pfizer, the manufacturer of varenicline, misreported adverse events to MedWatch associated with the drug, thus skewing the evidence for the drug's safety.[31]

60. The most recent (2013) Cochrane Collaboration review of smoking cessation drugs concluded there was no evidence to link varenicline use with significantly greater neuropsychiatric events (including depression and suicide ideation) than a placebo. The review's authors concluded however that:

> Long-term post-marketing surveillance should continue for varenicline, to determine the likelihood of its implication in neuropsychiatric [...] cardiac events.[32]

61. This conclusion is consistent with two of the main schools of thought regarding varenicline. The first is that more data is needed on adverse events associated with the drug, before establishing an association (let alone a causal link) between varenicline and suicidality.[33] The second is that although existing study data does not provide much evidence for the link, the large volume of individual case reports from PMS programs and other sources means that health practitioners should be cautious in prescribing it to people suffering mental ill health and should carefully monitor patients for adverse reactions to the drug.[34]

Evaluation of evidence

62. The potential link between varenicline and suicidality has been examined by several expert research groups internationally, who have used a variety of different research designs. To date no consensus has been reached on the question of whether or not varenicline can cause suicidality in patients.

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[31] Kuehn BM, "New Reports Examine Psychiatric Risks of Varenicline for Smoking Cessation", *Journal of the American Medical Association*, vol 307, no 2, 11 January 2012, p.129.

[32] Cahill K, et al, "Pharmacological interventions for smoking cessation: an overview and network meta-analysis (Review)", *The Cochrane Collaboration*, 2013, p.26.

[33] See for example Stapleton J,"Do the 10 UK suicides among those taking the smoking cessation drug varenicline suggest a causal link?", *Addiction*, vol 104, 2009, p.865;

[34] Purvis TL, et al, "Varenicline use in patients with mental illness: an update of the evidence", *Expert Opinion on Drug Safety*, vol 9, no 3, 2010, pp.479-480; Harrison-Woolrych M, Ashton J, "Psychiatric Adverse Events Associated with Varenicline", *Drug Safety*, vol 34, no 9, 2011, p.771;

Evaluation of varenicline prescribing

63. As explained above, varenicline is an authority-required medication on the PBS, and its authority-required clinical criteria and treatment criteria effectively comprise a prescribing guideline. If the clinical and treatment criteria were re-framed in a guideline format, they would read as follows:

    a. varenicline must only be prescribed as an aid to achieving abstinence from smoking, and not for any other purpose;

    b. varenicline must not be prescribed in conjunction with any other drug therapy for nicotine dependence;

    c. varenicline must only be prescribed to patients who have indicated they are ready to cease smoking;

    d. the patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time the practitioner intends to commence prescribing varenicline. Details of the support and counselling must be documented in the patient's medical records; and

    e. clinical review of the patient should occur within two to three weeks of commencing varenicline.

National Prescribing Service (NPS) guideline

64. In August 2011 the NPS produced advice on varenicline prescribing to assist practitioners. The document was not a guideline as such, but provided a range of evidence-based advice consistent with a guideline. The central elements in the advice addressing suicidality and mental ill health were:

    a. varenicline should be avoided for patients with serious psychiatric illness, because "serious psychiatrist events" have been reported in people treated with varenicline;

    b. counselling and support should be provided for patients who wish to stop smoking and who are prescribed varenicline;

c. patients should be advised about possible serious adverse psychiatric effects associated with varenicline, including depressed mood, hallucinations, anxiety, psychosis, and suicidal thoughts and suicide attempts. There are reports of symptoms being exacerbated with varenicline, as well as new-onset symptoms; and

d. a patient check-up should occur within two to three weeks after varenicline is commenced, and again after the treatment is completed, to check for unusual or serious changes in the patient's mood or behaviour.[35]

Royal Australian College of General Practitioners (RACGP) guideline

65. In June 2012 the RACGP published its guideline titled *Supporting Smoking Cessation: A Guide for Health Professionals*. The guideline included a detailed consideration of pharmacotherapies for smoking cessation (nicotine replacement therapy, bupropion and varenicline). Varenicline was recommended as a first-line treatment for smoking cessation, with the following guidance:

> Clinical suitability
>
> Not recommended in pregnancy and childhood. Caution with significant intercurrent psychological/psychiatric disease. Caution in cardiovascular disease. Nausea in 30% of patients. Reduce dose in severe renal impairment (check PI)
>
> Patient choice
>
> Reasons to prefer:
>
> - on current evidence, varenicline is the most effective pharmacotherapy;
> - PBS subsidy; and
> - lack of drug interactions.
>
> Treatment algorithm
>
> - give initial four-week script; arrange for return for second script and discussion of progress;
> - encourage use of support services;
> - at follow up, review progress and problems: common adverse effects, nausea and abnormal dreams;
> - check for neuropsychiatric symptoms;

[35] National Prescribing Service, "Varenicline (Champix) for smoking cessation", NPS Radar, August 2011.

- encourage completion of 12 weeks of therapy;
- if quit, further 12 weeks available on PBS to reduce relapse; and
- consider a further follow up visit if patient needs extra support.[36]

66. Additional clarification regarding the above guidance included:

    a. varenicline's safety has not been established in patients with psychiatric conditions, so caution is urged with these patients;

    b. there have been post-market reports of mood change, depression and suicidal ideation possibly associated with varenicline, so prescribers are advised to monitor patients for these symptoms; and

    c. prescribers should ask patients to report any mood or behaviour changes after commencing varenicline, and advise patients to stop varenicline at the first sign of any of these symptoms.[37]

67. In July 2014, the RACGP published an updated version of the guideline. The basic information regarding varenicline (including the clinical suitability, patient choice and treatment algorithm material set out above) did not change, however there were some changes in the additional information. Specifically, the 2014 guideline significantly softened the discussion on potential links between varenicline, mood changes, depression, behavioural disturbance and suicidal ideation, noting that these links "are so far not substantiated" by evidence.[38]

Appropriateness of the prescribing

Dr Kwiatek

68. Dr Kwiatek's varenicline prescribing is not germane to my investigation, given it occurred some two years before Mr Gilbett's death; however for the sake of completeness, I have briefly considered it.

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[36] Zwar N, et al, *Supporting Smoking Cessation: A Guide for Health Professionals*, Royal Australian College of General Practitioners, July 2012, p.19.

[37] Zwar N, et al, *Supporting Smoking Cessation: A Guide for Health Professionals*, Royal Australian College of General Practitioners, July 2012, p.27.

[38] Zwar N, et al, *Supporting Smoking Cessation: A Guide for Health Professionals*, Royal Australian College of General Practitioners, July 2014, p.28.

69. As discussed, Dr Kwiatek prescribed varenicline while treating Mr Gilbett at the Plenty Valley Medical Centre on 17 August 2009. At this time, neither the NPS nor the RACGP guideline was available, and therefore only the PBS authority required criteria would have been relevant to his prescribing. Addressing the criteria in order:

    a. Dr Kwiatek prescribed the varenicline for smoking cessation;

    b. there is no evidence Dr Kwaitek prescribed any other pharmacotherapy in conjunction with the varenicline for smoking cessation;

    c. Dr Kwiatek's notation "Counselling abstinence willingness" presumably means John Gilbett had indicated he was ready to quit smoking;

    d. there is no evidence that Dr Kwiatek provided counselling to Mr Gilbett concurrently with the course of varenicline treatment. If counselling was provided, it was not documented in Mr Gilbett's medical records; and

    e. there is no evidence in Mr Gilbett's medical records that Dr Kwiatek reviewed his clinical progress within two to three weeks of commencing varenicline (or at any time after 17 August 2009).

70. On the evidence available to me it would appear that Dr Kwiatek did not prescribe the varenicline consistently with the PBS authority required criteria.

Dr Deady's 22 February 2011 prescribing

71. Dr Deady prescribed varenicline while treating John Gilbett on 22 February 2011 at the Epping Plaza Medical and Dental Centre. At this time, neither the NPS nor the RACGP guideline was available, and therefore only the PBS authority required criteria would have been relevant to his prescribing. Applying these criteria:

    a. Dr Deady prescribed the varenicline for smoking cessation;

    b. there is no evidence Dr Deady prescribed any other pharmacotherapy in conjunction with the varenicline for smoking cessation;

    c. Dr Deady wrote in his medical records: "Wants to QUIT many options disc. Try Champ disc. Long disc also re meds etc." Presumably this means Mr Gilbett indicated he was ready to quit smoking;

d. there is no evidence in Mr Gilbett's medical records that Dr Deady provided counselling to him concurrently with the course of varenicline treatment. However in Dr Deady's subsequent Coronial Brief statement he wrote that Mr Gilbett "was doing quite well on this but stopped on his own accord around March, as he had an altercation with his wife to whom he was married for about 24 years and she asked him to leave the house." This is potentially evidence that counselling and discussion occurred, even if it wasn't documented in the medical records; and

e. there is no evidence in Mr Gilbett's medical records that Dr Deady reviewed his clinical progress within two to three weeks of commencing varenicline, though again the Coronial Brief statement potentially indicates that such review did take place.

Mr Gilbett's August 2011 recommencement

72. Mr Gilbett's patient-initiated recommencement of varenicline in late August 2011 is a scenario that does not appear to have been contemplated in the PBS authority required criteria, nor in the NPS or the RACGP guidelines.

73. With respect to the PBS authority required criteria, I assume that a patient-initiated recommencement of varenicline would probably require the doctor to respond by recommencing the patient on a concurrent counselling program. There is no evidence in the medical records that Dr Deady did this (assuming such a program had been put in place back in February 2011), however the medical records do show that both Dr Deady and Dr Wong discussed the varenicline with Mr Gilbett, which potentially could comprise 'counselling'.

74. The contents of any counselling are pertinent at this stage because the NPS prescribing advice was published in August 2011, probably just before Mr Gilbett announced he had recommenced his varenicline. The NPS advice included that patients should be warned about possible adverse psychiatric effects associated with varenicline, and a patient check-up should occur within two to three weeks to check for unusual or serious changes in the patient's mood or behaviour. Accepting Mera Gilbett's evidence on the change in Mr Gilbett's mood after recommencement, this clinical advice and follow-up recommendation might have been important.

COMMENTS

Pursuant to section 67(3) of the **Coroners Act 2008**, I make the following comment(s) connected with the death:

75. The lack of detail in the medical records makes it difficult to determine whether

    a. Dr Deady commenced John Gilbett on varenicline consistently with the PBS authority required criteria; and

    b. Dr Deady's clinical response upon learning Mr Gilbett had self recommenced the varenicline was consistent with the PBS authority required criteria and the NPS advice.

76. Beyond the question of adherence to clinical advice and guidelines sits the more general question of whether the varenicline prescribing could be causally linked to Mr Gilbett's decline in mental state and suicide. As has been discussed in some depth above, no causal link is broadly supported by the research literature (though its potential existence is acknowledged). Additionally, any consideration of whether the varenicline caused Mr Gilbett's suicidality must also include consideration of the other significant stressors he was experiencing, such as:

    a. chronic opioid dependence;

    b. chronic non-malignant pain that was not relieved by drug therapy;

    c. chronic mental illness; and

    d. separation from his wife.

77. I note there are significant gaps in the available medical material for Mr Gilbett, which poses significant challenges in assessing Mera Gilbett's evidence regarding her ex-husband's sudden mental decline.

FINDINGS

The lack of toxicological analysis' ability to detect varenicline (and a subsequent inability to established whether Mr Gilbett had used varenicline at any time proximal to death), together with the lack of empirical evidence linking varenicline with suicidality limit my ability to identify Mr Gilbett's possible consumption of varenicline as a causal factor in his death.

It does not appear that Mr Gilbett was warned about possible adverse psychiatric effects associated with varenicline pursuant to the recently published NPS prescribing advice when he reported self-recommencing varenicline to Dr Deady on 31 August 2011. I am unable to say however that the lack of warning was in any way causal to Mr Gilbett's death and I accordingly make no adverse findings in this regard.

A number of contributing factors have been identified that may have influenced Mr Gilbett's decision to adopt the course of action he ultimately chose. Precipitating factors include chronic opioid dependence, chronic pain not relieved by drug therapy, chronic mental illness and separation from his wife.

I accept and adopt the medical cause of death as identified by Dr Malcolm Dodd and find that Mr John Raymond Gilbett died from hanging in circumstances where I am satisfied that he intended to take his own life.

FINAL COMMENT

The apparent copious amount of local and international reports and anecdotal evidence gleaned from my investigation should not necessarily be dismissed. I therefore forward my Findings to the TGA to consider the circumstances of Mr Gilbett's death, and the totality of my investigation, to consider whether his death can be considered a suspected adverse reaction to varenicline.

I acknowledge the extensive research and synthesis of data performed by the Coroners Prevention Unit.

Pursuant to section 73(1) of the **Coroners Act 2008**, I order that the following be published on the internet.

I direct that a copy of this finding be provided to the following:

Ms Carolyn Kovac, Maurice Blackburn Lawyers on behalf of Mrs Mera Gilbett

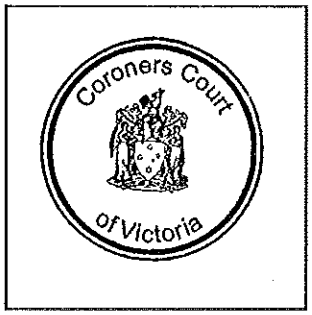
Dr Kee Wong

Mrs Danielle Middleton, Transport Accident Commission

Therapeutic Goods Administration

Senior Constable Cameron Caine

Signature:



AUDREY JAMIESON
CORONER
Date: **12 December 2014**