IN THE CORONERS COURT
OF VICTORIA
AT MELBOURNE

Court Reference: COR 2015 1002

FINDING INTO DEATH WITHOUT INQUEST

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

I, JACQUI HAWKINS, Coroner having investigated the death of Benjamin David Johnston

without holding an inquest:
find that the identity of the deceased was Benjamin David Johnston
born on 17 October 1978
and the death occurred on 28 February 2015
at Frankston Hospital, 2 Hastings Road, Frankston, Victoria, 3199
from:

1(a) GLOBAL HYPOXIC BRAIN INJURY
1(b) HANGING

Pursuant to section 67(1) of the **Coroners Act 2008**, I make findings with respect to **the following circumstances**:

1. Benjamin Johnston was 36 years old at the time of his death. He lived with his partner of 12 years, Lindy Hosking and step-son in Langwarrin.

2. Mr Johnston owned his own garden maintenance business and was described by Ms Hosking to be a hard worker. Mr Johnston was a heavy smoker and drank six to eight cans of alcohol about four or five times per week.

3. Ms Hosking noted that six weeks prior to his death, Mr Johnston had made a decision to quit smoking because he wanted to lead a healthier and better life. His grandfather had emphysema from smoking and Mr Johnston did not want to become unwell as he got older. Mr Johnston was determined to quit smoking and told everyone that he had quit.

4. Ms Hosking was aware that Mr Johnston had been prescribed Varenicline (also known as Champix)[1] and that it can affect people's mind and their mental state.

5. Ms Hosking reported that two weeks before Mr Johnston's death she had noticed a change in his behaviour. He had become withdrawn, tended to get angry more easily than usual, he was highly irritable and prone to argue. He also had difficulty sleeping.

Medical History

6. In November 2010, Mr Johnston reported to Dr Kilner Brasier at the Young Street Medical Clinic, Frankston, that he had been depressed for a number of years. He was feeling down, complained of loss of interest in life, helplessness and insomnia. He requested to see a psychologist. Later that month, he saw Dr Robert Kruk, Psychiatrist, who reported to Dr Brasier in May 2011 that he had seen Mr Johnston on one occasion and he had not returned for follow up, as requested.

7. On 19 December 2014, Mr Johnston attended the Young Street Medical Clinic and saw Dr Saul Solomon and requested help to quit smoking. Dr Solomon referred to Mr Johnston's medical records and noted his history of depression in 2010.

8. Dr Solomon reported Mr Johnston was agreeable to trying varenicline however before he prescribed it, he assessed Mr Johnston for depression and found no signs or symptoms. Dr Solomon reported he explained the possible side effects of varenicline, including depression. He also reported he would have warned Mr Johnston that if he developed any side effects from varenicline, to stop taking it and inform him immediately.

9. Dr Solomon next saw Mr Johnston on 6 January 2015, for an unrelated problem. At the time, there were no signs of depression. Dr Solomon last saw Mr Johnston on 26 January 2015. He prescribed a repeat of varenicline. Dr Solomon reported that again, Mr Johnston did not display any symptoms or signs of depression. He asked Mr Johnston to return for a follow up in 10 days.

Surrounding Circumstances

10. On 22 February 2015, Mr Johnston went to work in the early morning. He returned home at approximately 1pm and Ms Hosking reported they had a discussion about their relationship. He then spent time in the garage and came out at around dinner time to give his step-son and

[1] For the purpose of consistency, I will refer to varenicline throughout this finding.

Ms Hosking money to buy dinner. Ms Hosking and her son went out to get dinner sometime between 8pm and 8.30pm.

11. At approximately 8.45pm, Ms Hosking received a text message from Mr Johnston saying 'I'm sorry'. Ms Hosking found this message out of character so she went out to the garage to look for Mr Johnston. The door was locked and she reported it was never locked. Ms Hosking went to her car and used her garage door remote to open the door. She walked around Mr Johnston's parked car and found him hanging by a rope attached to the rafters. She called for her son for assistance and they attempted to lift Mr Johnston. Neighbours heard her calls and came to help. They lowered Mr Johnston to the ground and at this time, Ms Hosking noticed Mr Johnston's car engine was running. Her neighbour assisted to move it out of the way and turn it off.

12. Ms Hosking's son called emergency services and they commenced cardiopulmonary resuscitation (CPR). Victoria Police arrived first and assisted with CPR before Ambulance Paramedics arrived and took over resuscitative efforts. Paramedics performed CPR and obtained a return of spontaneous circulation.

13. Mr Johnston was transported to the Frankston Hospital Emergency Department. He was admitted to the Intensive Care Unit (ICU) and underwent cardiac cooling. A computed tomography (CT) scan of the brain showed no acute intracranial abnormality and a chest x-ray did not identify any rib fractures. Following completion of cardiac cooling, Mr Johnston became febrile and had radiological changes in the right lower base of the lung, suggestive of aspiration pneumonia and he was started on intravenous antibiotics.

14. Nursing staff noted Mr Johnston was having myoclonic jerks. On examination by medical staff, these were believed to be secondary to pain or sensation, however all brain stem functions were intact. The myoclonic jerks increased and the neurology team conducted an electroencephalogram (EEG)[2] which showed widespread seizure activity during the myoclonic jerks. A magnetic resonance imaging (MRI) of Mr Johnston's brain was also conducted which was suggestive of global hypoxic ischaemic injury.

15. Following discussions with Mr Johnston's family and treating clinicians, the decision was made to withdraw active treatment and Mr Johnston passed away on 28 February 2015.

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[2] Is a test that detects electrical activity in the brain using small, flat metal discs (electrodes) attached to the scalp.

CORONIAL INVESTIGATION

16. The circumstances of Mr Johnston's death have been the subject of investigation by Victoria Police. On 22 February 2015, after Mr Johnston was taken to Frankston Hospital, Police conducted a search of the garage. They located hand written notes on a bench. These notes evidenced Mr Johnston's intention to take his own life. There was also evidence on Mr Johnston's computer that he had searched how to tie a noose.

17. Also located in the garage was an empty packet of varenicline medication that was prescribed to Mr Johnston. The investigation did not identify any suspicious circumstances.

Forensic medical investigation

18. On 3 March 2015, Dr Jacqueline Lee, Forensic Pathologist at the Victorian Institute of Forensic Medicine (VIFM) performed an external examination on the body of Mr Johnston, reviewed the post mortem CT scan and the Form 83 Victorian Police Report of Death. Mr Johnston was an organ donor and all his organs and tissues were donated to Donate Life.

19. Toxicological analysis of ante-mortem blood retrieved in hospital on 23 February 2015, revealed the presence of alcohol (0.11g/100mL) and midazolam (0.04mg/L)[3]

20. Dr Lee provided an opinion that the medical cause of death as 1(a) COMPLICATIONS OF HANGING.

21. Having considered all of the evidence, I have determined to amend the cause of death to 1(a) GLOBAL HYPOXIC BRAIN INJURY, 1(b) HANGING.

Family concerns

22. At the time Mr Johnston's body was admitted to the VIFM for the forensic medical investigation, Ms Hosking raised the issue of Mr Johnston's recent use of varenicline and requested that we investigate the possible link to his death.

23. On 5 March 2015, Ms Susan Davies, aunt of Mr Johnston wrote to the Coroners Court and urged me to investigate the circumstances of Mr Johnston's death and the potential link with varenicline. Further, she urged that varenicline should be banned from sale.

24. On 24 March 2015, Mrs Keryn Johnston, Mr Johnston's mother wrote to the Coroners Court. Mr Johnston reported that:

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[3] This drug was most likely administered by emergency/hospital staff.

He decided to get his life back on track, quit smoking and eat healthier. He went to his doctor who prescribed a drug called Champix which apparently has a good success rate with helping to give up smoking. This was about the beginning of January 2015 when he started taking it. He suffered from hallucinations and lack of sleep but persevered with the drug.

25. Mrs Johnston also stated that she had spoken to her son on the evening of his death and she said that he was not suicidal that night or any night in the six years prior to his death. She stated "I strongly believe that the drug Champix caused his mind to lose control. Ben's death was not suicide but an accident brought on by this drug."

26. Mrs Johnston advised that she was writing to inform me of the family's concerns and to prevent this drug being prescribed so readily by doctors.

Further toxicological testing

27. As a result of these family concerns, and as part of the coronial investigation, I requested the VIFM to conduct further toxicological testing and specifically test for the presence of varenicline. At the time VIFM did not routinely test for this drug.

28. A supplementary toxicology report was provided to me on 19 November 2015 which revealed the presence of 2ng/mL of varenicline in Mr Johnston's ante-mortem blood sample taken by the Frankston Hospital on 23 February 2015.

Investigations conducted into the manufacture and sale of varenicline in Australia

Coroners Prevention Unit Report

29. After I received the coronial brief of evidence, I determined to conduct further investigations into Mr Johnston's death by requesting information from the Coroners Prevention Unit (CPU)[4] in relation to the purported link between varenicline and suicidality and requesting information from Pfizer Australia Pty Ltd (Pfizer), the manufacturer of Champix, which is their product name for varenicline and the Therapeutic Goods Administration (TGA) in relation to the legal requirements around the sale of varenicline, which I outline in detail below.

30. 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

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

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.[5] 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.[6]

31. Varenicline is marketed in Australia by Pfizer under the brand name Champix. In February 2007, the TGA approved it for use as "an aid for 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.[7] 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.[8]

How varenicline is prescribed and taken

32. 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

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5 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.

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

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

8 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.

c. the patient must have indicated they are ready to cease smoking.[9]

33. The varenicline commencement authority-required treatment criteria are that 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 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 initiated. Clinical review is recommended within 2 to 3 weeks of the initial prescription being requested.[10]

34. 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.[11]

35. The varenicline continuation authority-required treatment criteria are that the:

> Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program.[12]

36. 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.

37. 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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[9] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 3 December 2015.

[10] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 3 December 2015.

[11] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 3 December 2015.

[12] Pharmaceutical Benefits Scheme "Varenicline", <http://pbs.gov.au/medicine/item/ 5469W-9128K-9129L>, accessed 3 December 2015.

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.[13]

Prescription of varenicline to Mr Johnston

38. The available material suggests that Mr Johnston was prescribed varenicline on two occasions. On the first occasion, Dr Solomon prescribed varenicline, the entry in the patient medical history reads:

> Keen to quit smoking. No recurrent depression. Discussed reasons for medication and possible side effects. Will join my time to quit. Review 1/12.

39. It appears this entry satisfies the authority-required treatment criteria. 'My Time to Quit' is a support program operated by Pfizer and is described as "a flexible online support program designed to help you open the door to quitting and boost your chances of success." To be eligible, consumers must have been prescribed a treatment for smoking cessation.

40. The accompanying prescription notation in the patient medical history indicated "1 – Champix (Combination pack)". This is the commencement package containing a combination of 11 tablets of 0.5mg varenicline and 42 tablets of 1mg varenicline.

41. The second occasion on which Mr Johnston was prescribed varenicline occurred on 26 January 2015. Dr Solomon's entry in the patient medical history relevant to varenicline reads "1) due for 2nd champix – has quit." Dr Soloman that at this consultation there were no symptoms or signs of depression.

42. The accompanying prescription notation in the patient medical history indicated "56 x 2 – Champix (Tablets) 1 mg." This is the continuation package that contains 56 tablets of 1mg varenicline.

Prescribing guidelines

National Prescribing Service (NPS) guideline

43. 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

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

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.[14]

Royal Australian College of General Practitioners (RACGP) guideline

44. In June 2012, the RACGP published its guideline titled *Supporting Smoking Cessation: A Guide for Health Professionals*. The guideline noted that:
    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.[15]
45. In July 2014, the RACGP published an updated version of the guideline. It 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.[16]

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[14] National Prescribing Service, "Varenicline (Champix) for smoking cessation", NPS Radar, August 2011.
[15] Zwar N, et al, *Supporting Smoking Cessation: A Guide for Health Professionals*, Royal Australian College of General Practitioners, July 2012, p.27.
[16] Zwar N, et al, *Supporting Smoking Cessation: A Guide for Health Professionals*, Royal Australian College of General Practitioners, July 2014, p.28.

Varenicline and suicidality

46. 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

47. 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.

48. 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.

49. In Australia, 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:

> <u>What to report? You don't need to be certain, just suspicious.</u>
>
> 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.[17]

50. 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",

[17] 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*.

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".[18]

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".[19]

51. In the United States of America (USA) the Food and Drug Administration (FDA) has issued several alerts regarding varenicline. In May 2008, the FDA announced "it appears increasingly likely that there is an association between [varenicline] and serious neuropsychiatric symptoms". In July 2009, a label warning was introduced and in 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.[20]

52. Alerts have also been made in the United Kingdom (UK). The Medicines and Healthcare Products Regulatory Agency (MHRA) issued an alert in July 2008, noting 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.[21]

53. In New Zealand in May 2009, a warning regarding suicidal ideation and changes in behaviour and mood was added to the packaging for varenicline dispensed in New Zealand. In May 2013, their PMS program published a report 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".[22]

Evidence from published research

54. 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:

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

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

[20] 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.

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

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

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 general population, and that smoking cessation is associated with depression and therefore potentially with increased suicide risk;[23]

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.[24] 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;[25]

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;[26]

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;[27] and

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[23] 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.

[24] 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.

[25] 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.

[26] 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.

[27] 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[28] associated with the drug, thus skewing the evidence for the drug's safety.[29]

55. 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.[30]

56. 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.[31] 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.[32]

Evaluation of evidence

57. 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.

Further investigation

58. Having considered the CPU Report, I determined that it would be appropriate to conduct further investigations and I sought information from the TGA and Pfizer.

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[28] The FDA's PMS program.

[29] 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.

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

[31] 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;

[32] 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;

Request for information from Therapeutic Goods Administration

59. The TGA advised it has no requirement for the product information (PI – a document about the medication, aimed primarily for healthcare professionals) or consumer medicine information (CMI – a document about the medicine, aimed primarily for consumers) for varenicline to be included in the packaging. The TGA does require that the CMI is made available to consumers in some form. It was reported many manufacturers of medicines include the CMI in the packaging. The CMI and PI are available on the TGA website.

60. The TGA advised that the strongest warning that can be placed on any medicine in Australia is a 'boxed warning'. In the USA this is called a 'black box warning' and is included in the equivalent of the PI (called the label). There are significant differences in how boxed warnings are used in Australia and the USA. In the USA it is used more extensively where in Australia similar product information is included in the contraindications and precautions section of the PI document. The information is also included in the CMI leaflet. The TGA advised it is currently considering a 'boxed warning' for varenicline to warn of neuropsychiatric adverse events.

61. The TGA has reviewed material concerning the relationship between varenicline use and neuropsychiatric events, including material supplied by the sponsor of varenicline and individual adverse event cases reported to the TGA. The TGA is satisfied that the varenicline PI accurately reflects this information.

62. The varenicline PI and CMI are required to be updated as new safety information becomes available. These documents currently contain information about the possibility of neuropsychiatric adverse events associated with the use of varenicline, including the need for prescribing doctors to discuss the possibility of these symptoms with patients and for patients' family/carer to be aware of this possibility. The TGA has twice published information about the possibility of neuropsychiatric adverse events with varenicline, firstly in the Australian Adverse Drug Reaction Bulletin, December 2008 and secondly in the Medicines Safety Update, August 2010. The TGA advised these two documents were widely distributed to healthcare professionals and are available on the TGA website.

Request for information from Pfizer

63. Pfizer were asked whether they were aware of any issues, concerns or problems associated with the use of varenicline. They responded by saying all medicines have benefits and risks.

These are assessed in conjunction with the TGA in the process of approving the drug and are then continually assessed, by both the sponsor as well as the TGA, after product approval.

64. After a drug is approved by the TGA and marketed, it continues to be surveyed, both by the TGA and the sponsor to ensure that the risk-benefit balance remains favourable for its continued use. As part of this process, Pfizer continues to evaluate its products following registration and accordingly, additional studies have been completed since registration and are reflected in the product information. Further, Pfizer reported they conduct numerous ongoing pharmacovigilance activities for the detection and evaluation of adverse events to provide safety monitoring commensurate with product characteristics and in accordance with local and international pharmacovigilance requirements and their ethical obligations. Signal detection activities include medical review of individual adverse event reports as well as periodic aggregate data review. Safety signal evaluation requires the collection and assessment of all available safety information to evaluate whether there is a potential causal link between an event and the administration of the product.

65. Periodic Safety Update Reports (PSURs) are produced by Pfizer Inc. and are made available to Pfizer country offices including Pfizer Australia for submission to the TGA as required. Any significant safety issues identified are communicated to the TGA in accordance with local regulations.

66. Furthermore, to address how safety concerns will be identified and mitigated once a product is available and to ensure that the benefit-risk balance remains favourable, Risk Management Plans (RMPs) are utilized. RMPs contain a description and analysis of the safety profile of the medicine including a summary of the safety concerns and a set of pharmacovigilance and risk minimisation activities designed to identify, characterise and manage risks relating to the medicine including the assessment of the effectiveness of these activities and interventions.

67. In addition to routine pharmacovigilance activities and the RMP, Pfizer provides materials to healthcare professionals that includes information such as product precautions, contraindications, interactions and adverse effects. In addition to materials directed to health care professionals such as the PI, information is made available to patients in the form of the CMI leaflet. In Australia the varenicline packaging also contains reference to the CMI and guidance to patients to speak to their doctor or pharmacist if they feel unwell while taking varenicline.

68. Pfizer reported it distributes the CMI electronically to pharmacists, who then provide this to the patients when a medicine is dispensed. The vast majority of CMIs in Australia are distributed electronically. Electronic distribution of CMIs to pharmacists is in accordance with legal requirements and ensures that patients receive the most current version of this document. The currency of the CMI would not be achieved by including the CMI in packaging.

69. Pfizer has compiled a comprehensive summary of clinical research related to neuropsychiatric effects and suicide. These documents are provided to health care professionals in response to queries and reflect a comprehensive summary of published literature. It was reported these documents are proactively updated to ensure that current and accurate information is available to health care professionals.

Recent Safety Advisory Notice from the TGA

70. On 2 December 2015, the TGA advised that the product information for varenicline has been updated with new safety information. This information relates to the risks of psychiatric symptoms and their potential interaction with alcohol. The PI includes the need to advise patients that consuming alcohol may increase the risk of psychiatric symptoms. It was reported that the updated PI aims to increase awareness that serious psychiatric symptoms have been reported in patients taking varenicline and to stress the importance of stopping treatment with varenicline and immediately contacting a health professional if these symptoms are experienced or observed. This information had previously been provided in the PI, but is now highlighted in bold text at the beginning of the precautions section under the heading 'Psychiatric Symptoms'.

71. It is noted that there are a number of other factors that can also contribute to psychiatric symptoms being reported in relation to treatment with varenicline, including the effects of nicotine withdrawal, existing psychiatric conditions and use of some other medicines. The updated PI also includes information from clinical trials and observational studies, which found similar incident rates of suicidal thoughts and/or behaviour, as well as other common psychiatric symptoms, in patients treated with varenicline as to those treated with placebo or alternative treatments.

FINDINGS

72. I find that Benjamin Johnston died on 28 February 2015 from *1(a) global hypoxic brain injury 1 (b) hanging.*

73. I find that toxicological analysis conducted on Mr Johnston's ante-mortem blood retrieved from the Frankston Hospital on 23 February 2015 detected ~2ng of varenicline.

74. I find that in the weeks prior to his death, the evidence reveals that Mr Johnston had been displaying altered behaviour, in that he had become withdrawn, angered easily and was irritable and more prone to anger. I further find that prior to this altered behaviour he had been well, was getting fit and making efforts to stop smoking and had commenced taking varenicline.

75. I find that on 22 February 2015, Mr Johnston had a blood alcohol content of 0.11g/100mL, had recently consumed varenicline, had written a note expressing his intention to end his life, and tied a rope around his neck and hanged himself with the intention of ending his life.

76. I acknowledge that there is some evidence linking the consumption of varenicline with adverse psychiatric symptoms including suicidal ideation or behaviour, however, to date, studies have failed to establish a causal link. I further note the recently updated product information for varenicline from the TGA advising that consuming alcohol may increase the risk of psychiatric symptoms.

77. I find the evidence supports that Mr Johnston's death was an adverse reaction to varenicline.

78. I make no criticism toward Dr Saul Solomon's prescribing of varenicline to Mr Johnston.

79. I am grateful to the Coroners Prevention Unit for the assistance they provided to me in relation to this investigation.

80. I acknowledge the grief and loss suffered by Mr Johnston's partner and family and I offer my sincerest condolences. I consider their requests for me to investigate the possible link to varenicline with Mr Johnston's death were most appropriate.

COMMENTS

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

81. As a consequence of Mr Johnston's death and two other recently completed coronial investigations[33] at the Coroners Court of Victoria, the Victorian Institute of Forensic Medicine have confirmed that they will shortly commence testing for varenicline as part of their routine toxicological analyses. This will hopefully assist with enhancing the evidentiary basis of the potential link between varenicline and suicidality. However, it seems more research and evidence is required before a causal link can be established.

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[33] Finding into death without Inquest of Alexander Thomas Domanski COR 2011 2074, Finding into death without Inquest of John Raymond Gilbett COR 2011 3420.

82. To assist with the improvement of knowledge in relation to a possible causal link between varenicline and suicide, I am forwarding my findings to the TGA and Pfizer as evidence that Mr Johnston's death was an adverse reaction to varenicline.

83. I reiterate that serious neuropsychiatric symptoms have occurred in patients being treated with varenicline. Patients and their families should be advised that the patient should stop taking varenicline and contact a health care professional immediately if they note changes in behaviour or thinking, agitation or depressed mood, that are not typical or if the patient develops suicidal ideation or suicidal behaviour. I also reiterate the latest safety advisory warning provided by the TGA that consuming alcohol with varenicline may increase the risk of psychiatric symptoms.

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

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

Ms Lindy Hosking
Mrs Keryn Johnston
Ms Susan Davies
Dr Saul Solomon
Therapeutic Goods Administration
Mr Kieran O'Brien, DLA Piper, on behalf of Pfizer Australia Pty Ltd
Dr Dimitri Gerostamoulos, Head of Forensic Sciences, VIFM
Births, Deaths and Marriages Victoria
Royal Australian College of General Practitioners
Senior Constable Stephen Ellis, Coroner's Investigator

Signature:

JACQUI HAWKINS
Coroner
Date: 9 December 2015