IN THE CORONERS COURT
OF VICTORIA
AT MELBOURNE

Court Reference: COR 2007 612

FINDING INTO DEATH WITH INQUEST

Form 37 Rule 60(1)
Section 67 of the ***Coroners Act 2008***

Inquest into the Death of:	IVO JOHN MARTINOV
Delivered On:	21 November 2013
Delivered At:	Level 11, 222 Exhibition Street Melbourne 3000
Hearing Dates:	7-10 February 2011
Findings of:	JANE HENDTLASS, CORONER
Representation:	MR J. GOETZ appeared on behalf of Dr N. Theoharidis & Dr X. Prodromou. MR C. WINNEKE appeared on behalf of Novartis Pharmaceutical.
Police Coronial Support Unit	Leading Senior Constable T. Cristiano

I, JANE HENDTLASS, Coroner having investigated the death of IVO (AKA) JOHN MARTINOV

AND having held an inquest in relation to this death on
at Melbourne
find that the identity of the deceased was IVO (AKA) JOHN MARTINOV
born on 24 May 1948
and the death occurred on 15 February 2007
at Unit 9, 41 Hudson Street, Coburg, Victoria, 3058
from:

1 (a) Unascertained causes

in the following circumstances:

1. John Martinov was 58 years old when he died. He lived in supported aged care accommodation at Unit 9, Irving Benson Court at 41 Hudson Street in Coburg. Irving Benson Court is an aged care facility administered by Wesley Mission Melbourne.

2. Mr Martinov had an intellectual disability and he had difficulty with verbal communication Mr Martinov also suffered from treatment resistant schizophrenia, obsessional shopping, gastro-oesophageal reflux and was overweight. In 2006, Mr Martinov was also diagnosed with non-insulin dependent diabetes.

3. Mr Martinov also smoked a packet of cigarettes a day and regularly drank excessive amounts of coffee and Coca Cola. He would have at least four coffees in the morning and a two-litre bottle of Coca Cola in the afternoon.

4. Mr Martinov was on a Disability Support Pension. His financial affairs were administered by the State Trustees and managed by Wesley Aged Care Housing Service. He was also in receipt of an Aged Care Package.

5. At Irving Benson Court, Mr Martinov received assistance with shopping, cleaning, washing, appointments and recreational activities including basketball. Staff also administered Mr Martinov's medication each morning and evening from a Webster pack prepared weekly by Sable Pharmacy.

6. Irving Benson Court staff said that Mr Martinov was a lovely man; he kept to himself but was kindly and concerned. Mr Martinov's sister, Anna Damjanic, agreed with this but also noted he could become violent earlier in his life before his condition stabilised.

7. Mr Martinov's general practitioner was Dr Nicholas Theoharidis. Dr Theoharidis managed Mr Martinov's diabetes, weight reduction and attempts at smoking cessation and ordered routine blood tests to monitor his physical health.

8. Mr Martinov's schizophrenia was managed by a consultant psychiatrist, Dr Xenia Prodromou. At the time of his death, she prescribed clozapine 700mg *nocte*, sertraline hydrochloride 100mg *mane* and omeprazol 20 mg daily.

9. Clozapine is an atypical anti-psychotic medication reserved as a last resort for otherwise treatment-resistant schizophrenia.

10. On 15 February 2007, Vicki Irvine administered Mr Martinov's medication from the Webster pack during the morning shift. Mr Martinov ate lunch in the dining room as normal. Ms Irvine does not recall anything out of the ordinary during her shift.

11. Ms Irvine was a Residential Support Worker from Wesley Aged Care Housing Service. She was a personal care attendant Level III and had undertaken additional training relating to dementia and medication.

12. At 5.10pm on 15 February 2007, Ernalia Casama gave Mr Martinov his evening medication, that is 700mg clozapine. Mr Martinov was in his pyjamas as usual. He seemed unwell and was perspiring heavily.

13. Ms Casama was another Residential Support Worker with Wesley Aged Care Housing Service. She had had completed a Certificate III in Disability and Aged Work. Ms Casama had regularly worked at Irving Benson Court since 2005.

14. At 5:40pm on 15 February 2007, Ms Casama found Mr Martinov unresponsive on the floor in his room. She contacted her Team Leader, Carol Stanton. Ms Stanton and the Manager, Susannah Dax, attended Mr Martinov's room together. Ms Dax was a registered Division 1 nurse.

15. Mr Martinov was unable to be revived.

16. The forensic pathologist who inspected the body was unable to form an opinion as to the cause of death.

17. Toxicological analysis of a blood sample taken on 19 February 2007 and analysed on 20 February 2007 detected 3.9 mg/L clozapine, 2.9mg/L desmethylclozapine and 0.5mg/L sertraline.

18. Following toxicological analysis, Professor David Ranson determined:

"The toxicology results show a high level of clozapine and the level detected is one which is capable of being toxic. It is therefore possible that this may have been a factor in this man's death although in the absence of a complete autopsy examination interpretation of the significance of such a level with respect to the cause of death is problematic."

19. At that time, the notes attached to the Victorian Institute of Forensic Medicine Toxicology Report advised that this level of clozapine was potentially toxic. Subsequent to Professor Ranson completing his inspection report, Clozapine Toxicity was entered into the coronial case management system as Mr Martinov's cause of death.

20. This finding will consider the circumstances and cause of Mr Martinov's death. Specifically, it will consider whether Mr Martinov's death can be attributed to clozapine toxicity.

Background

21. Since 1967, Mr Martinov had suffered from treatment resistant schizophrenia. He was first admitted to a psychiatric hospital when he was 25 years old and was in and out of institutions for much of his life.

22. Over the course of his condition, Mr Martinov was prescribed various medications to manage his schizophrenia. From at least 2002 (but perhaps as early as 1996[1]), his psychiatrists prescribed 700mg per day clozapine.

23. In 2000, Mr Martinov's mental state was stable. He was discharged from a Community Treatment Order and became a voluntary mental health patient. He lived in a residential unit in Broadmeadows and maintained a therapeutic connection with the North West Area Mental Health through the Moreland Continuing Care Program

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1 The Adverse Event report from Glencairn Consulting Suites to Novartis indicates that Mr Martinov commenced Clozapine on 15 February 1996 however further information about this is not known.

24. On 11 March 2002, Mr Martinov moved to live at Irving Benson Court.

25. Since 22 April 2002, Dr Nicholas Theoharidis had been Mr Martinov's general practitioner. He managed Mr Martinov's diabetes, weight reduction and smoking cessation and ordered routine blood tests to monitor his physical health. At first Mr Martinov remained under psychiatric supervision from Moreland Continuing Care Program.

26. On 19 February 2004, Mr Martinov was still experiencing auditory hallucinations, paranoia and marked cognitive deficits. He was being prescribed clozapine 700mg *nocte* and sertraline 100mg *mane*. However, Dr Prassanna, consultant psychiatrist from the Moreland Continuing Care Program, referred Mr Martinov to a private consultant psychiatrist, Dr Xenia Prodromou, for ongoing psychiatric management.

27. Dr Prassanna transferred Mr Martinov from public psychiatry services to private psychiatry because, although he continued to express low grade residual psychotic symptoms, he no longer presented with any major ongoing psychosocial risk issues that warranted his continued involvement with the Moreland Continuing Care Program.

28. Dr Prodromou treated Mr Martinov from 19 February 2004 until his death. She described Mr Martinov's mental illness as follows:

"He had ongoing positive symptoms of psychosis (auditory hallucinations and paranoid delusions) in addition to marked negative symptoms (emotional blunting, impoverished thinking, reduced social contact), in addition to marked cognitive impairment (poor concentration and memory, slowed mentation and reduced intellect).

29. Dr Prodromou continued to prescribe clozapine 700mg *nocte* and sertraline 100mg *mane* for Mr Martinov. She told the Court that she did not alter the doses of these medications during her treatment of Mr Martinov because his mental state remained stable.

30. Dr Prodromou also prescribed omeprazole for Mr Martinov to treat gastro-oesophageal reflux. Omeprazole is often co-prescribed to people taking clozapine.

31. As part of the requirements for prescribing clozapine, Mr Martinov was required to have full blood examinations every 28 days and annual echocardiograms.

32. Dr Prodromou routinely ordered and reviewed Mr Martinov's full blood examinations. They were never abnormal.

33. On 19 May 2006, Mr Martinov had also his last echocardiogram. The left ventrical was normal size and systolic function, with an ejection fraction of more than 59% (normal). Mild atrial enlargement was noted but this is not known to be associated with clozapine toxicity.

34. Dr Theoharidis was aware Mr Martinov was seeing Dr Prodromou monthly for his psychiatric needs including medication and counselling. However, Dr Prodromou did not regularly communicate the blood and echocardiogram results to Dr Theoharidis. Dr Theoharidis considered that there was no need to be in touch with Dr Prodromou because he was not in a shared-care arrangement.

35. Further, Dr Theoharidis attended annual case conferences about Mr Martinov with Ms Dax, Matthew Wong from Sables Pharmacy, and Gayl Lawson, the Care Coordinator at Irving Benson Court.

36. On 1 July 2006, following one of these case management meetings, Matthew Wong undertook to write up a Comprehensive Medication Management Report. Mr Wong's report suggested that Dr Theoharidis also arrange routine blood sugar levels and an electrocardiogram for Mr Martinov. These tests led to his diagnosis with diabetes, but otherwise, they were normal.

37. Mr Martinov last attended Dr Theoharidis on 24 January 2007 for routine blood tests. Mr Martinov had been well on previous visits and continued to present well at this consultation.

38. Dr Theoharidis ordered his routine full blood examination and an electrocardiogram. The results were well within the normal range.

39. On 12 February 2007, Mr Martinov's further full blood examination remained within the normal range.

40. On 13 February 2007, Mr Martinov last saw Dr Prodromou. Dr Prodromou says his mental state remained stable. Dr Prodromou continued to prescribe 700mg clozapine *nocte*, Zoloft 100mg *mane* and omeprazole 20 mg daily.

Circumstances of Mr Martinov's death

41. On 15 February 2007, medication charts show that Ms Irvine dispensed Mr Martinov's medication from the Webster pack in the morning. Ms Irvine does not remember giving Mr Martinov his medication on this day.

42. Wesley Aged Care protocol was for two staff members to check the Webster pack to ensure that the names fitted the photographs on file. There are no records to confirm that these checks took place. The staff providing the medication were personal care attendants, not registered nurses.

43. However, Ms Dax noted that, if the Webster pack had be incorrectly dispensed, then the Mr Marinov's medication doses would be wrong. The staff were experienced with each patient and would notice a difference in their medication. If anything happened when administering the medication, an incident report would be prepared and staff were very good at doing this.

44. Similarly, at 5:10pm on 15 February 2007, Ms Casama dispensed his evening medication from the Webster pack and watched him swallow it. She initialled Mr Martinov's records for his evening medication. Ms Casama had also dispensed these medications from the Webster pack on 31 January, 1, 2, 3, 4 and 14 February 2007 as well as on 15 February and on previous occasions. She was well aware of the medication she usually dispensed for Mr Martinov. Ms Casama did not notice any difference from usual in Mr Martinov's medication.

45. However, Ms Casama noted that Mr Martinov seemed unwell because he was perspiring profusely. She asked if he had just had a shower. He did not reply but this was not considered unusual.

46. It was a hot day (approximately 40 degrees Celsius) and his presentation could have been attributed to this. Mr Martinov did not have air conditioning in his room but he had a fan on his bedside table.

47. Ms Casama left Mr Martinov's room to continue providing the residents with their medication. After she had finished, Ms Casama prepared and began to distribute soup to the residents.

48. At 5:40pm, Ms Casama returned to Mr Martinov's room to give him his soup. She could not find him at first but the toilet door was closed so she thought that he might be in there. She called out to him that his soup was ready but she did not receive a response.

49. As Ms Casama walked behind the table, she found Mr Martinov unresponsive on the floor. He seemed to have already died.

50. Mr Martinov was unable to be revived.

51. Professor David Ranson prepared the inspection report based on his external examination of Mr Martinov and his post mortem toxicology results. In the absence of an autopsy, Professor Ranson was unable to ascertain the cause of Mr Martinov's death.

52. Further, Professor Ranson denied entering Clozapine Toxicity in the Coroners Court computer system as the cause of death. He was unable to explain to the Court how this alteration occurred without his authorisation.

COMMENTS

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

1. John Martinov was 58 years old when he died. He lived at Irving Benson Court which is supported aged care accommodation located at 41 Hudson Street in Coburg and administered by Wesley Mission Melbourne.

2. Mr Martinov had an intellectual disability and suffered from treatment-resistant schizophrenia, obsessional shopping and gastro oesophageal reflux. He was also a recently diagnosed non-insulin dependent diabetic, overweight and a smoker.

3. At 5:40pm on 15 February 2007, Mr Martinov was found unresponsive in his room at Irving Benson Court about 30 minutes after having been administered his nightly medication.

4. No autopsy was performed. Although a potentially toxic level of clozapine was found in Mr Martinov's blood post-mortem, the cause of his death was unable to be ascertained. However, the cause of death in the Coroners Court computer system was recorded as Clozapine Toxicity. I remain unable to explain how this entry occurred.

5. This unexplained entry of Clozapine Toxicity in the Coroners Court computer system led to my decision to focus my investigation on whether Mr Martinov's cause of death could be attributed to clozapine toxicity, including an analysis of the regulatory framework for the prescription and use of clozapine as it applied to Mr Martinov.

6. In addition to the toxicology and forensic pathology reports and medical records, I received information, assistance, and expert advice from a number people with respect the Mr Martinov's medical management and possible cause of death. These included:

- Professor Burrows who is a Professorial Fellow in the Department of Psychiatry at the University of Melbourne and is Chairman of the Section of Psychiatry for the Australian Medical Association (Victoria);

- Professor Nicholas Keks who is Director of Education and Research at Delmont Private Hospital, Professor of Psychiatry at Monash University, and Head of Clinical Research Unit of the Mental Health Research Institute of Victoria;

- Professor Olaf Drummer who is the Head (Forensic Scientific Services) at the Victorian Institute of Forensic Medicine, Adjunct Professor and Head of the Department of Forensic Medicine at Monash University, with over 25 years experience in the analysis of drugs and poisons and the interpretation of their biological effects;

- Dr Duflou who is a Specialist Forensic Pathologist, Chief Forensic Pathologist of the Department of Forensic Medicine in Sydney, Clinical Professor in the Central Clinical School of the University of Sydney, Conjoint Associate Professor in the School of Medical Sciences and the National Drug and Alcohol Research Centre of the University of New South Wales; and

- George Lillis who is Head of Regulatory Affairs (Australia and New Zealand) at Novartis Pharmaceuticals Australia (Pty Ltd).

Clozapine prescription and monitoring

7. Clozapine is an atypical anti-psychotic drug of the dibenzodiazepine class used to manage treatment-resistant schizophrenia. It has been supplied in Australia since March 1993.

8. Professor Keks told the Court that clozapine was 20% more effective than other medications in treating schizophrenia.

9. However, use of clozapine can be associated with a number of serious side effects.

10. The packaging of clozapine has five black box warnings[2] relating to:

    - Agranulocytosis - an abnormally low white blood cell count. Since white blood cells are necessary to fight infections, this is a potentially fatal side effect;

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2 A black box warning appears on the label of a prescription medication to alert patients and health care staff about any important safety concerns, such as serious side effects or life-threatening risks. It is the sternest warning for medication.

- Seizures;
- Myocarditis - inflammation of heart muscle; and
- Other adverse cardiovascular and respiratory effects.

11. In Australia, clozapine use is also associated with development of acute myocarditis and cardiomyopathy in some individuals with increased mortality in elderly patients with dementia.

12. Accordingly, use, prescription, and dispensing of clozapine is heavily regulated by the Commonwealth Highly Specialised Drugs Program.[3]

13. Therefore, clozapine is reserved for individuals like Mr Martinov who fail to respond to other anti-psychotic medications and who meet on-going strict eligibility criteria, including acceptable white blood cell and neurophil counts, imposed by the Therapeutic Goods Administration.

14. Further, in Victoria, there are only two suppliers of clozapine: Hospira Pty. Ltd., Melbourne, Victoria, which markets clozapine as Clopine; and Novartis Pharmaceuticals Australia Pty. Ltd, North Ryde, New South Wales which markets clozapine as Clozaril.

15. Medical practitioners who prescribe clozapine must be registered with either Hospira or Novartis and can only prescribe that specific brand of clozapine. Glencairn Consulting Suites was a registered centre with Novartis and accordingly, Mr Martinov was prescribed Clozaril. The prescription of Clozaril must be in accordance with Novartis protocols.

16. The Clozaril Patient Advice Leaflet also says:

> *"In severe cases, some deaths have occurred. It is important that you understand the importance of strict and regular checks by your doctor while taking Clozaril.*
>
> *If at any stage of your treatment with Clozaril you develop a sore throat, mouth ulcers or a fever, contact your psychiatrist immediately for a blood test. This is necessary as these symptoms may be an early indicator of agranulocytosis."*

17. The Novartis protocols include the Clozaril Patient Monitoring System. The Clozaril Patient Monitoring System requires all patients, doctors, medical officers, pharmacists, centre co-

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3 Commonwealth Highly Specialised Drugs Program, Victoria, Australia.

ordinators and treating centres involved in the distribution of Clozaril to be registered with the Clozaril Patient Monitoring System.

18. The Clozaril Patient Monitoring System specifies that Clozaril can only continue to be prescribed if the patient's history, physical examination and full blood examinations are satisfactory. A full blood examination must be conducted before every prescription of clozapine is issued. For the first 18 weeks after commencing clozapine, the patients' blood patterns must be monitored weekly and monthly monitoring should occur thereafter.

19. The Court heard that the practical infrastructure required to ensure patients and prescribers comply with administration of these criteria restricted clozapine prescribing to public patients and patients of larger psychiatry practices.

20. Mr Martinov was prescribed clozapine from at least November 2002 but it is possible that he was prescribed it as early as 1996.[4]

21. Dr Xenia Prodromou was at all relevant times a medical practitioner registered to prescribe Clozaril. Although a note on 9 September 2002 in the Wesley file and copied to the Theoharidis file indicates that Mr Martinov's Clozaril was to be prescribed by Dr Theoharidis, the records from the Pharmaceutical Benefits Scheme indicate that this never occurred.

22. When Mr Martinov was transferred to the care of Dr Prodromou, he was being prescribed 700mg *nocte*.

23. On 26 March 2004, Mr Martinov's serum clozapine level was reported to be 1093ng/ml (1.09mg/L), 13 hours after the last dose. This test was to establish a baseline of clozapine concentration in Mr Martinov's blood. This was higher than recommended therapeutic clozapine levels but Mr Martinov was not exhibiting symptoms of toxicity and was otherwise psychiatrically stable. Therefore, Dr Prodromou continued to prescribe 700mg clozapine *nocte*.

24. The Court heard that the usual dose of clozapine is 300–600 mg per day. However, some patients require divided doses of up to 900 mg per day to achieve the required effect.

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4 The Adverse Event report from Glencairn Consulting Suites to Novartis indicates that Mr Martinov commenced Clozapine on 15 February 1996.

25. These higher doses can be particularly useful with patients who smoke, as there is evidence that this lowers the blood levels of clozapine. Novartis recommend that medical practitioners titrate the dosage down to the lowest therapeutic dose, however the evidence given at inquest was that this did not occur for Mr Martinov.

26. Dr Prodromou noted at inquest:

"Initially when he consulted me, I did not think it was appropriate to change the dose of the drug that he had been deemed stable on and managed by a community care team for considerable period of time. Over the time he consulted me his mental state really changed very little. He did exhibit clear, ongoing symptoms of his illness."

27. Further, although Mr Martinov's clozapine dose was outside the usual recommended maximum dose of 600mg daily, all the experts providing evidence in this coronial enquiry considered it to be within appropriate prescribing practice because his psychosis remained stable over a long period of time.

28. Further, Mr Martinov underwent routine monthly blood tests from 6 November 2002. He was always within the normal range.

29. Patients prescribed clozapine are also required to have cardiac tests, including electrocardiographs, troponin levels and echocardiograms six months following the first prescription of clozapine and yearly thereafter. None of the cardiac tests performed on Mr Martinov revealed anything that indicated deterioration associated with clozapine.

30. The experts also considered prescription of clozapine in a single rather than split dose was acceptable practice. Some medical practitioners prescribe a single dose above 600mg to be taken at night to prevent the patient feeling tired during the day as a result of the sedative effects of clozapine.

31. No serum levels were collected or analysed for Mr Martinov after 26 March 2004.

32. I heard consistent evidence that, in isolation, plasma levels of clozapine are not a true indicator of risk to the patient. Professor Drummer told the Court:

"There is no clear correlation between a plasma concentration, a blood concentration and an outcome, such an adverse reaction."[5]

33. This is supported by the literature, for example, Greenwood-Smith et al (2003) who noted:

"Due to its complex metabolism, there are significant inter- and intra individual variations in clozapine serum levels, for a given dose. However, the range of serum levels that corresponds with toxicity remains unclear."

[...] The current literature does not support the routine testing of serum clozapine levels in everyday clinical practice".[6]

34. The Court experts agreed that analysis of plasma levels might be indicated if there was concern about compliance. However, in the absence of specific indications, it would be reasonable not to collect serum levels subsequent to establishing a baseline.

35. In particular, Dr Lillis was of the opinion that monitoring of clozapine levels would not be useful for medical practitioners to identify toxicity. He noted:

"Yeah, I guess, what my view is that the monitoring of plasma levels of clozapine, at best, would be of limited clinical value."

36. Nevertheless, Dr Lillis said there might be instances that warrant re-testing:

"I think, there may be instances when a plasma level is warranted. I mean, if you need to understand if a patient is being compliant with their medicine because a lot of patients may not, necessarily, take their medicine and you may want to know if they are taking their medicine, so that would be one instance, perhaps."

37. Professor Drummer also advocated determining serum levels on an *ad hoc* basis where there was evidence suggesting toxicity:

"If the patient perhaps develops some signs of toxicity or adverse affects that were perhaps cause for concern, then there might be a need to see whether levels are high and might be

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5 Professor Olaf Drummer, Transcript 9 February 2011, page 83.

6 Greenwood-Smith C, Lubman DI & Castle DJ (2003). Serum clozapine levels: a review of their clinical utility. Journal of Psychopharmacology; 17(2): 231-235.

cause of that if the patient was unable to remove the drug as easily as somebody else, for example."

38. Accordingly I make no recommendations for introducing routine clozapine analyses as part of the monitoring of patients prescribed clozapine to manage otherwise treatment-resistant schizophrenia.

39. The Clozaril Patient Monitoring System has a process for monitoring and following up on adverse events[7] that occur while a patient is taking clozapine.

40. In this Clozaril Patient Monitoring System, each patient is recorded in the system by a number and their initials and any person who becomes aware of an adverse event occurring while the patient is treated with Clozaril should report that event within 24 hours to Novartis Clinical Safety and Epidemiology so that Novartis can make appropriate follow up enquiries.

41. The Clozaril Patient Monitoring System reports verified adverse events to the relevant health authorities, including the Therapeutic Goods Association and to the global drug safety database administered by Novartis.

42. The first report of an adverse event received by Novartis for Mr Martinov related to his death.[8]

43. The overwhelming consensus between the witnesses at inquest was that Mr Martinov was treated appropriately and all precautions were taken with respect to the prescription and monitoring of clozapine.

44. Dr Keks, for example, considered that Dr Prodromou's treatment of Mr Martinov was consistent with a manner widely accepted by colleagues of good repute and standing as competent professional practice in the treatment of a patient with chronic treatment-resistant schizophrenia.

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7 Adverse events include such things as the manifestation of side effects, white blood cell and neutrophil counts outside of the normal range, irregular echocardiographs and death.

8 The initial report of his death made on 7 March 2007 contained an incorrect patient reference (and no other personal identifiers) which resulted in the death incorrectly being recorded for a female patient at the Glencairn Consulting Suites.

45. Similarly, in response to the question whether Dr Prodromou's treatment of Mr Martinov was appropriate, Professor Burrows said: "*Definitely yes*" and that it would appear from the information available to him that the dosage and monitoring were both adequate.

46. Dr Duflou said that Mr Martinov's myocardial function and his blood count were monitored on a regular basis in accordance with best practice guidelines.

47. With respect to the processes and procedures in place for the prescription and monitoring of clozapine, Professor Burrows gave evidence that:

"I could say we can always improve things and so I'm not disagreeing with you, Your Honour, but there's no good in the world literature at the moment any good science to say that what we're doing at the moment needs significant changing."[9]

48. Professor Keks noted:

"[...] as clozapine is the most effective medication available for the treatment of severe treatment-resistant schizophrenia (a profoundly devastating disease with its own risks including mortality), use of clozapine is universally regarded as justified in appropriate circumstances."

49. Accordingly, I find that the treatment and monitoring of Mr Martinov's mental and physical health whilst taking clozapine was appropriate and consistent with the guidelines imposed by the Therapeutic Goods Administration and Novartis.

50. Further, in the absence of any inconsistent analytical results, I find that Mr Martinov's routine clozapine dose over at least five years and probably longer did not cause the drug to accumulate to a toxic level and did not contribute to his death.

51. Moreover, the evidence suggests that clozapine was a useful and effective drug in the management of Mr Martinov's schizophrenia, which had previously been resistant to treatment. Although residual symptoms remained, Mr Martinov's mental state had been stable for many years.

52. Further, all the experts before me endorsed easing the system that restricts availability of clozapine for patients with otherwise treatment-resistant schizophrenia. I also note that, in

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9 Evidence of Professor Burrows, Transcript of Proceedings, Page 112.

advocating easier access to clozapine, they added the proviso that it may be too late to make a difference because of the new drugs coming on to the market.

53. However, I am also aware that the relevant expertise of these eminent psychiatrists arose because they were all clozapine prescribers. Therefore, I feel unable to further encourage its use without hearing the views of a wider section of psychiatry. Accordingly, I make no recommendation on this issue.

Clozapine overdose

54. Acute overdose with clozapine can cause agitation, dystonia, central nervous system depression, tachycardia and death.

55. The short time between Mr Martinov's death and his taking his afternoon medication means that I cannot exclude the possibility that the two events were causally related.

56. This could occur if Mr Martinov was given the wrong clozapine dose on 15 February 2007.

57. In turn, the wrong dose could occur if the staff medicated Mr Martinov from the wrong person's Webster box or the Webster box had been wrongly compiled. Both of these circumstances seem unlikely.

58. In particular, the staff members working on 15 February 2007 knew Mr Martinov well. They provided him with his clozapine medication from the Webster box in the evenings and watched to ensure he swallowed it so that the medication was not stockpiled. Ms Casama indicated that she gave Mr Martinov his medication regularly and would have noticed if it was more than usual.

59. Further, Irving Benson Court staff undertook random audits of a few Webster packs each time to see whether they had the correct number of tablets. The tablets were checked against descriptions of the medication on the back of the Webster pack. There are no records to confirm that these checks took place but there are records of the medications being provided to Mr Martinov.

60. Ms Irvine noted that she had only found the wrong amount of tablets from Sables Pharmacy on three occasions in three years that she worked during day. She reported this to the coordinator on each occasion.

61. Ms Dax indicated that the coordinator was very efficient and there was very little that she would not pick up on.

62. Further, Mr Martinov was already on a high dose of clozapine so that no other patient was likely to be prescribed significantly more than he was. Therefore, a mix-up in clozapine dose with another patient is unlikely to have resulted in changing Mr Martinov's response and causing his death.

63. Professor Olaf Drummer stated:

"If he was on a stable dose and had not shown signs of toxicity then death from this drug is less likely."

64. I therefore find that it is unlikely that Mr Martinov received an incorrect dose on or in the lead up to 15 February 2007.

65. Accordingly, in circumstances where Mr Martinov was displaying symptoms of severe stress prior to taking his medication and he had been taking the same drug at the same dose for many years without demonstrable side effects, I find that Mr Martinov's death was only circumstantially related to recent administration of his evening dose of clozapine.

66. I also considered the possibility and impact of clozapine accumulating in Mr Martinov's blood over time.

67. The variable relationship between clozapine serum levels and toxic effects was explained by Professor Keks who noted:

"a high level of variability is routinely observed and apparently high concentrations may not be associated with serious adverse effects, while at times low concentrations can be associated with serious problems such as convulsions."

68. Further, Professor Drummer indicated in his expert opinion that chronic use of clozapine would lead both to some accumulation of the drug and the development of tolerance. At inquest, however, he clarified this:

"Look, what I meant by that is that the blood concentration from the single dose and no other doses will be a lot lower at any given time point than if a patient is on a constant daily or twice daily dose because there is some accumulation in the body normally over the first week

and then it plateaus out. It goes up and down depending on the time of day but it is higher than the patient's first dose if you'd use the same dose.[10]

69. Professor Keks noted that symptoms and signs of accumulated clozapine toxicity are usually not subtle and he found no information to indicate that Mr Martinov was in a distressed physical or psychological state in the hours to days before his death. He stated:

"Specifically, when seen by Dr Prodromou on February 13, his cognitive dysfunction was unchanged from previously, and characteristic of his chronic schizophrenic state. There were no indications of drowsiness or delirium (which can also be described as confusion), which would be expected if clozapine toxicity had developed."[11]

70. Professor Keks further noted that:

"In my opinion it was most unlikely that Mr Martinov was experiencing manifestations of excessive clozapine dosing in the days prior to his death. As indicated above, this conclusion is based to some degree on assumptions, because there is no mention of manifestations of toxicity in reports."[12]

71. Mr Martinov did not exhibit physical symptoms of toxicity and his medical tests were consistent with no toxicity in blood tests on 10 February 2007 and on 12 February 2007.

72. The electrocardiogram ordered by Dr Theoharidis to monitor Mr Martinov's physical health on 10 February 2007 also revealed no abnormalities.

73. Accordingly, I also find that it is not likely that clozapine had accumulated to the point of toxicity.

74. Given this, it was necessary to consider whether the level of clozapine identified post-mortem was in fact an accurate reflection of his steady-state ante-mortem levels. The evidence I obtained confirmed my suspicion that it was not.

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10 Professor Olaf Drummer, Transcript 9 February 2011.

11 Expert opinion of Professor Keks, Page 5.

12 Expert opinion of Professor Keks, Page 6.

75. It was always difficult to interpret potentially toxic levels of clozapine post-mortem in determining their contribution to the cause of Mr Martinov's death. Factors making the interpretation more difficult include:

- the variability between plasma levels of clozapine and toxic effects;
- post-mortem redistribution resulting from the interval between death the sample being taken and analysed; and
- that no autopsy occurred.

76. Each of these will now be discussed in turn.

77. Mr Martinov consumed his last dose of clozapine approximately half an hour prior to his death.

78. Professor Drummer gave evidence of the trough concentrations (the point at which the concentration of the drug in the plasma is the lowest). He said this would usually occur shortly before the next dose was due. Therefore, in twice daily dosing, the trough is usually approximately 12 hours after the initial dose. However, in a daily dosing, the trough is most likely to be just before the daily dose.

79. Therefore, Mr Martinov's clozapine concentration would have reached a trough approximately half an hour prior to his death and, for the half hour after consuming the tablets, Mr Martinov would have been absorbing and metabolising the clozapine into his system.

80. Professor Keks noted that:

"Clozapine is absorbed rapidly from the gastro-intestinal tract. It is possible to reach peak serum concentrations within half an hour of ingestion, although 2 to 3 hours is more usual. Nonetheless, baseline clozapine concentrations undergo rapid elevation following a dose of clozapine, possibly increasing two to three fold".

81. He went on to say:

"A blood sample taken shortly after administration of clozapine will therefore produce a high concentration, which does not reflect the steady state 12 hour trough concentration. It cannot be regarded as indicative of the steady state trough concentration which is measured 12 hours after drug ingestion"

82. In addition, individuals absorb and metabolise clozapine at varying rates. A recent research article noted that there could be up to 50-fold variation in the rate of metabolism between patients.[13] Peak blood concentrations of clozapine can occur anywhere between 0.5 and 4 hours after dosing.

83. Therefore, I am unable to determine how much clozapine Mr Martinov had absorbed and metabolised in the 30 minutes prior to his death and cannot even use this as an indicator of his clozapine serum concentration at death.

84. Of even greater concern is that the drug redistribution process which occurs after death makes the interpretation of the post-mortem clozapine concentration impossible. This is particularly so in Mr Martinov's case, because the sample of blood used for the post-mortem toxicological analysis was taken on 19 February 2007 and analysed on 20 February 2007, 3 and 4 days after death respectively.

85. Professor Drummer said:

"So not all drugs will have been absorbed in one hour, most likely, you know, but a fair bit would have been but it would be drug from previous doses and unfortunately, and there's always a frustration from my point of view, is that post mortem there'll always be increases for these sorts of drugs because the concentrations of clozapine and more clozapine in muscle tissue and fat tissue surrounding a blood vessel, whether it being a leg or anywhere else, is much, much higher than the - time of death."[14]

86. He explained further:

"So when the tissue then dies, it leaks and drug defusing from high to low concentration and so you get that increase that you can't stop."

87. The levels in Mr Martinov's case would be especially influenced by this process because of his obesity. Clozapine is lipophilic and Mr Martinov had more than normal fat deposits which would have stored clozapine and released some of it after his death as his body fluids re-distributed towards equilibrium.

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13 Couchman L., Morgan P.E., Spencer E.P., Flanagan R.J (2010) Plasma clozapine, norclozapine, and the clozapine:norclozapine ration in relation to prescribed dose and other factors: Data from a therapeutic drug monitoring service, 1993-2007. Ther Drug Monit 32(4); 438-447.

14 Professor Olaf Drummer, Transcript 9 February 2011, page 89.

88. This means that the sample taken from Mr Martinov post-mortem cannot be used as an indicator of his ante-mortem clozapine levels. De Leon and Simpson (2004) concluded:

"We do not believe that our present state of knowledge permits us to firmly extrapolate ante-mortem levels from post-mortem levels or to use post-mortem clozapine levels to claim a causal relationship to death"[15]

89. Accordingly, I find that the levels of clozapine detected post-mortem are of no value in determining the actual level of clozapine in blood at the time of death unless they are so high as to be overwhelming. This was not the case for Mr Martinov.

90. I have also considered the possibility that Mr Martinov's other drugs interacted with the clozapine, including the prescribed drugs of sertraline and omeprazole and the non-prescription drugs of nicotine and caffeine.

91. The Clozaril Product Information sheet produced by Novartis says that clozapine serum levels and associated toxicity may be increased with the concomitant use of sertraline. Conversely, omeprazole is usually associated with a reduction in clozapine concentrations.

92. Dr Lillis discussed the possibility of clozapine interacting with sertraline and omeprazole. In his opinion:

"[Mr Martinov] was reportedly on stable doses suggesting that no dose adjustment was needed and no interaction [with sertraline or omeprazole] suspected."

93. In addition, Professor Drummer noted that they only interact mildly with each other:

"It would have a contribution to play but because the two drugs are there, it wouldn't be appropriate to simply say at least an additive effect. The drugs are safe when administered together in ordinary circumstances".

94. Nicotine and caffeine are both thought to reduce the concentration of clozapine in the blood.

95. Accordingly, I find that it is possible all of the drugs consumed by Mr Martinov interacted with clozapine by either increasing or decreasing the serum concentration. However, given that these factors were consistent for a long time prior to Mr Martinov's death, it is unlikely

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15 Letter to the Editors – 'Postmortem Clozapine Levels' (2004) Journal of Clinical Psychopharmacology: February 2004, Volume 24, Issue 1, Pages 100-101.

that they interacted in a way that produced toxic effects on 15 February 2007. I therefore find that their interaction with clozapine was probably not a factor in Mr Martinov's death.

96. These general issues with interpretation of the toxicology results are compounded in Mr Martinov's case by the inability to exclude alternative causes of death because no autopsy was conducted.

97. Although all of the experts concluded that clozapine toxicity was unlikely to have caused Mr Martinov's death, they were also not prepared to exclude the possibility that it contributed to the death.

98. Professor Keks concluded:

"While acute clozapine toxicity cannot be entirely excluded as a cause for Mr Martinov's distress shortly before his death, in my opinion, it is also quite unlikely."

99. Professor Burrows noted:

"I am of the opinion that the cause of Mr Martinov's death would be very unlikely to be clozapine toxicity. He had been on a stable dose of the mediation, he had been monitored regularly, there had been no adverse effects recorded. I would have thought the other issues in his health including NIDDM, being overweight and a heavy smoker are more likely to be factors in his death than clozapine."

100. Dr Duflou similarly concluded:

"It is therefore unlikely, in my view, that the deceased died suddenly of any drug related (and specifically clozapine related) side effects as detailed above. [...]

"I conclude that although the level of clozapine and its metabolite found in this case are within the generally reported lethal range or self-administered overdose, there is no evidence to support a conclusion that the deceased died of an overdose of the drug in this case, given he was on steady high doses of the drug without observable side-effects."

101. The experts also could not formulate a definitive alternative cause of Mr Martinov's death. Professor Ranson clarified his position as follows:

"I mean that's essentially saying what I'm saying, that I don't believe I can find an unequivocal medical cause of death in this case.

102. This was supported by Professor Duflou:

"On its own, the levels of clozapine in this case cannot be interpreted. I therefore agree with the views expressed by Professor Ranson and Dr Lillis. The absence of an autopsy in this case makes an accurate determination of cause of death impossible, and conclusive interpretation of toxicology results is simply not possible in a case such as this without exclusion of other causes of death."[16]

103. Professor Duflou went on to say:

"The deceased had significant natural disease, in the form of diabetes mellitus and obesity, and when taken together with his smoking history, would certainly have placed him at high risk of atherosclerotic cardiovascular disease."

104. Atherosclerotic cardiovascular disease would have exposed Mr Martinov to possible sudden death with minimal or no proceeding symptoms. Professor Duflou also noted that although atherosclerotic cardiovascular disease was the most likely natural cause of death, there were a number of other natural causes that could also not be excluded.

105. I therefore find that Mr Martinov did not die of clozapine toxicity. Moreover, I cannot find that he died of any other specific cause (natural or otherwise). Therefore, I find that Mr Martinov died from unascertained causes.

106. As investigators, coroners rely on the information provided to them from the Victorian Institute of Forensic Medicine, including information contained in the toxicology reports.

107. This investigation was triggered by the now rejected inclusion of clozapine toxicity as the cause of death in Mr Martinov's coronial file. I do not know how this occurred. Professor Ranson certainly rejects the possibility that he authorised its use.

108. However, over the course of my investigation, I became concerned that the standard form comments included as an explanation of clozapine levels were insufficient to adequately alert me or others interested in risk assessment to the risks associated with interpreting how those levels might have impacted on Mr Martinov's death.

109. Specifically, I found that the comments created an impression of fatal toxicity, even though the level of clozapine was relatively low, no autopsy had been performed, and there exists

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16 Expert opinion of Professor Duflou, page 7.

significant inter and intra variability of clozapine levels associated with toxic effects. Accordingly, I suggested that these comments be revised.

110. As a result of my investigation into this death, the Victorian Institute of Forensic Medicine have modified the comments included in their toxicology reports to indicate more clearly problems with the interpretation of clozapine especially where no autopsy has been conducted. The comments also specify the difficulty with interpreting serum levels for clozapine, given the significant overlap between lethal and therapeutic concentrations.

111. I am satisfied that the comments included in Victorian Institute of Forensic Medicine toxicology reports now provide greater clarity with respect to the interpretation of post-mortem clozapine levels. At best, they act as an indicator that the deceased has taken the medication.

112. However, I emphasise the importance of taking great care when using this type of information and I advocate for vigilance in the detection of anomalies. Accordingly, I make no recommendations in relation to the way in which elevated post-mortem levels of clozapine are now reported by the Victorian Institute of Forensic Medicine.

RECOMMENDATIONS

Pursuant to section 72(2) of the **Coroners Act 2008**, I make no recommendations connected with the death.

Signature:

DR JANE HENDTLASS
CORONER
Date: **21 November 2013**