FORM 37

Rule 60(1)

REDACTED FINDING INTO DEATH WITH INQUEST

*Section 67 of the **Coroners Act 2008***

Court Reference: 1141/2009

Inquest into the Death of PC

Delivered On:	23 August 2010
Delivered At:	Shepparton
Hearing Dates:	23 August 2010
Findings of:	Annabel Hawkins
Place of death:	Tatura

FORM 37

Rule 60(1)

REDACTED FINDING INTO DEATH WITH INQUEST

Section 67 of the ***Coroners Act 2008***

Court Reference: 1141/2009

In the Coroners Court of Victoria at Shepparton

I Annabel Hawkins, Coroner having investigated the death of:

Details of deceased:

Surname:	C
First name:	P
*Address:	[REDACTED]

AND having held an inquest in relation to this death on 23 August 2010

at Shepparton Coroner's Court

find that the identity of the deceased was PC

and death occurred on 21st February 2009

at Tatura

from

1a PULMONARY OEDEMA DUE TO ACUTE ON CHRONIC HEART FAILURE RESULTING FROM A DOTHIEPIN OVERDOSE

in the following circumstances:

Background

P was a 20-year-old man who lived with his parents in Tatura. On Saturday afternoon, 21 February 2009, Mrs C found her son P lying face down on his bed, cold and unresponsive. An empty foil pack for an unnamed prescription drug was located on the floor beside him. Three unopened packets and one empty packet of Dothiepin 75 mg tablets (brand name Dothep) were found in his room, along with a partly consumed packet of Amoxycillin tablets (brand name Clamoxyl Duo Forte 875/125). When paramedics arrived they were unable to resuscitate him.

Forensic pathologist Dr Sam Rambaldo of the Victorian Institute for Forensic Medicine performed a post-mortem examination and determined the medical cause of death for P as pulmonary oedema due to acute on chronic heart failure resulting from a Dothiepin overdose.

An inquest was held at Shepparton on 23 August 2010. The following witnesses gave oral evidence:

- Dr Gerastamoulos

- Dr Jenny Sanders
- Dr Christopher Percival
- Dr Phillip Lu

P had a complex history of substance use and mental illness dating back to when he was approximately 16 years of age. Major features of this history included the following:

- In July 2005 P experienced a suspected psychotic episode while drinking and using marijuana heavily. He received counselling from psychologist Mr John Miksad for mood issues and substance use. General practitioner Dr Jennifer Sanders diagnosed him with depression and anxiety, and prescribed Fluoxetine (brand name Lovan), a selective serotonin reuptake inhibitor antidepressant.
- In July 2006 general practitioner Dr Yamei Cui, who works at the same medical centre as Dr Sanders, prescribed the hypnotic Zolpidem (brand name Stilnox) to treat P for insomnia.
- In November 2006 Dr Sanders referred P to psychiatrist Dr Indranil Chakrabahti, but it appears that P did not attend this appointment.
- In December 2006 Dr Sanders commenced P on Venlafaxine (brand name Efexor), a serotonin-norepinephrine reuptake inhibitor antidepressant. He experienced side-effects and stopped taking the drug in approximately October 2007.
- In January 2008 Dr Sanders commenced P on Fluvoxamine (brand name Movox), an SSRI antidepressant, to treat his depression and anxiety. However P again experienced side-effects. Consequently, in February 2008 Dr Sanders ceased the Fluvoxamine and prescribed him the anxiolytic benzodiazepine Alprazolam (brand name Xanax).
- In May 2008 Dr Sanders referred P to psychiatrist Dr Chris Percival, who diagnosed him as having a depressive illness that underpinned his illicit drug use. He recorded that P had recently used a range of drugs beyond marijuana including methamphetamine, dexamphetamine and gamma-hydroxybutyric acid.
- In July 2008 Dr Percival commenced P on Dothiepin (brand name Dothep), a tricyclic antidepressant, to treat depression as well as possible anxiety and suicidal ideation.
- In January 2009 Dr Sanders was concerned that P might be paranoid as well as anxious and depressed. The therapeutic relationship between P and Dr Percival had broken down some months previous, so Dr Sanders attempted to refer him to some other psychiatrists and psychologists, but nothing eventuated from this.
- P's last contact with the medical system was on 19 February 2009, when he saw general practitioner Dr Phillip Lu (who works at the same medical centre as Dr Sanders) about a sore throat. Dr Lu diagnosed a chest infection and prescribed him Amoxycillin tablets. On the same day, four packets of 30 Dothiepin 75 mg tablets (brand

name Dothep) were dispensed to P in line with an ongoing prescription to treat his depression.

Dothiepin

Dothiepin is a tricyclic antidepressant (TCA).[1] TCAs inhibit the reuptake of certain neurotransmitters, and this is thought (though not known) to be the basis of their antidepressant effect. TCA use can be accompanied (particularly at larger doses) by a number of toxic side-effects that appear to be due to both neurotransmitter reuptake inhibition and cardiac sodium channel blocking; these include cardiac problems, hypertension, respiratory depression, coma and convulsions. Cardiac arrest is the most common fatal result of TCA poisoning.[2]

(a) Australian medications containing Dothiepin

In Australia, Dothiepin is available in tablet and capsule form under the following brand names:

- **Dothep**, which is available in 25mg (capsule) and 75 mg (tablet) Dothiepin Hydrochloride dose strengths. It reaches peak concentration in the blood approximately 3 hours after ingestion.
- **Prothiaden**, which is available in 25mg (capsule) and 75 mg (tablet) Dothiepin Hydrochloride dose strengths. It reaches peak concentration in the blood approximately 3 hours after ingestion.

Australia's Therapeutic Goods Administration (TGA) approved both Dothep and Prothiaden for treatment of major depression in July 2003. An Australian Adverse Drug Reactions Bulletin in 2004 noted that approved indications for the 75mg doses of Dothiepin had been limited to the maintenance treatment of major depression.[3] The TGA approval for Dothep 75 mg tablets included a specific indication that they "are indicated only for the maintenance treatment of major depression"; no such indication was specified for Prothiaden 75 mg tablets.[4]

1 The term 'tricyclic' refers to the chemical structure of the molecule, which has three rings of atoms.

2 MIMS Australia, "Prothiaden: MIMS Full Prescribing Information", 1 September 2008, p.1; Sharon C Cheetham and David J Heal, "Antidepressant and anxiolytic drugs", in *Biological Psychiatry: Principles of Molecular Biology Volume 14*, Edited by Bittar and Bittar, Stamford: JAI Press, 2000, pp.515-516; Patrick E McKinney and Robin Rasmussen, "Reversal of Severe Tricyclic Antidepressant–Induced Cardiotoxicity With Intravenous Hypertonic Saline Solution", *Annals of Emergency Medicine*, vol 42, no 1, July 2003, p.21.Shane Darke and Joanne Ross, "The use of antidepressants among injecting drug users in Sydney, Australia", *Addiction*, vol 95, no 3, 2000, p.408 Robert Flanagan, "Fatal toxicity of drugs used in psychiatry", *Human Psychopharmacology: Clinical and Experimental*, vol 23, January 2008, p.46

3 Adverse Drug Reactions Advisory Committee, "Warning for High Dose Tricyclic Antidepressants", Australian Adverse Drug Reactions Bulletin, vol 23, no 5, October 2004.

4 This information was sourced from Therapeutic Goods Administration, Department of Health and Ageing, Australian Government, *Australian*

Under the Therapeutic Guidelines,[5] Dothiepin is additionally recommended as a treatment for generalised non-inflammatory chronic pain syndrome. For example, the Therapeutic Guidelines note that:

> Some antidepressants may improve pain, tenderness and sleep function in some patients [...]. A suitable progression would be: [...] dothiepin 25 mg orally, in the early evening, increasing the daily dose by 25 mg monthly up to a continuing dose of 75 mg each evening.[6]

(b) Dothiepin prescription rates in Australia and Victoria

Table 1 shows the annual number of prescriptions for Dothiepin in Victoria and Australia, as processed by Medicare Australia for the period 2000-2009 through the Pharmaceutical Benefit Scheme (PBS) and Repatriation Pharmaceutical Benefit Scheme (RPBS).[7] It demonstrates a noticeable decline in the number of prescriptions between these years; the number of Australian prescriptions issued in 2009 was 55% of the number issued in 2000, and similarly the number of Victorian prescriptions issued in 2009 was approximately 50% of the number issued in 2000.

This decline in the number of annual prescription for Dothiepin is consistent with a general global trend away from TCAs towards the two newer antidepressant classes, the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[8]

Table 1: Annual number of prescriptions for Prothiaden and Dothep in Victoria and Australia wide, as processed by Medicare Australia.

	Victoria	Australia
2000	175,647	731,690
2001	165,546	699,457
2002	151,068	649,615
2003	134,836	587,224

Register of Therapeutic Goods, <http://www.tga.gov.au/docs/html/artg.htm>, accessed 2 December 2010.

5 The Therapeutic Guidelines are published by non-profit organisation Therapeutic Guidelines Limited, and are widely used in the Australian medical community. They present independent information on best practice for treatment of a wide range of conditions. The Therapeutic Guidelines are endorsed by a number of peak Australian medical bodies including the Royal Australian College of General Practitioners, the National Prescribing Service, Royal College of Nursing Australia, and the Society of Hospital Pharmacists of Australia.

6 Therapeutic Guidelines Limited (eTG Complete), "Generalised noninflammatory chronic pain syndrome (including fibromyalgia)", October 2010.

7 Information accessed via Medicare Australia, Australian Government, *Pharmaceutical Benefits Schedule Item Reports*, <https://www.medicareaustralia.gov.au/statistics/ pbs_item.shtml>, accessed 31 August 2010.

8 Flanagan, "Fatal toxicity of drugs used in psychiatry", p.48.

2004	125,796	557,600
2005	116,201	515,836
2006	107,315	477,253
2007	99,476	448,948
2008	90,950	411,959
2009	90,553	403,707

(c) Dothiepin toxicity and death

Dothiepin's toxic effects include cardiac problems, hypertension, respiratory depression, coma and convulsions. Cardiac arrest is the most common fatal result of Dothiepin poisoning. The notable features of Dothiepin toxicity are described here.

- Dothiepin is highly toxic relative to other antidepressants

A range of research internationally suggests that TCAs are more toxic in overdose than the other three major classes of antidepressants. For example, a recent study found that among patients presenting at Victorian emergency departments with antidepressant poisoning, those who were suffering TCA toxicity scored higher in poisoning severity and were admitted more often than patients presenting with poisoning caused by other classes of antidepressant.[9]

Concomitant with this finding, there are reports from a number of researchers that TCA poisoning is also associated with a greater fatality rate than poisoning by other types of antidepressants. Specifically, several studies reported that people who overdosed on TCAs were more likely to die than people who overdosed on other types of antidepressants such as SSRIs.[10] One study found that those prescribed TCAs experienced a higher ratio of fatal antidepressant poisonings per million prescriptions than those prescribed monoamine oxidase inhibitors (MAOIs) or SSRIs.[11] The most commonly proposed explanation for this finding is that TCAs are inherently more toxic than other antidepressants;[12] however this explanation is not universally accepted.[13]

9 Anselm Wong, et al., "Changing epidemiology of intentional antidepressant drug overdose in Victoria, Australia", *Australian and New Zealand Journal of Psychiatry*, vol 44, no 8, August 2010, p.763.

10 Shitij Kapur, et al., "Antidepressant Medications and the Relative Risk of Suicide Attempt and Suicide", *Journal of the American Medical Association*, vol 268, no 24, December 1992, p.3441; J Guy Edwards, "Suicide and antidepressants: Controversies on prevention, provocation, and selfpoisoning continue", *British Medical Journal*, vol 310, 28 January 2008, p.205.

11 John A Henry, et al., "Relative mortality from overdose ofantidepressants", *British Medical Journal*, vol 310, 28 January 1995, p.221.

12 Robert D Gibbons, et al., "The Relationship Between Antidepressant Medication Use and Rate of Suicide", *Archives of General Psychiatry*, vol 62, February 2005, p.171. Specifically, it is argued that TCAs are far more cardiotoxic than other antidepressants. In ranking the toxicity of the most commonly used antidepressants, TCAs are generally identified as the most toxic, followed by MAOIs, with SSRIs and SNRIs the least toxic. See for example

Among the TCAs, Dothiepin is frequently singled out as being associated with a particularly high incidence of toxicity and death. Several studies report that those prescribed Dothiepin experience a significantly higher ratio of fatal antidepressant poisonings per million prescriptions, than those prescribed other antidepressants.[14] The comparably higher toxicity of Dothiepin in contrast with other TCAs (as well as other types of antidepressants) appears to be an intrinsic characteristic of the drug; it is independent of ingested dose, characteristics of the patient and whether or not it is co-ingested with other substances.[15] For these reasons, as early as 1989 experts expressed concern that Dothiepin presented an unacceptable risk of death to patients.[16]

- **Dothiepin can interact with other drugs to produce toxic effects**

Dothiepin interacts with a number of drugs to potentiate (intensify) their action. Specific warnings have been issued for the potentiating effect of Dothiepin on the following types of drugs:

- Alcohol;
- Barbiturates;
- Tranquillisers and other central nervous system depressants;
- Anti-epileptics; and
- Anticholinergics.

Further, Dothiepin might block the antihypertensive effect of adrenergic neuron blocking drugs, and it increases the risk of postural hypotension when used simultaneously with diuretics. Finally, a potentially lethal interaction can occur between Dothiepin and MAOIs or other TCAs.[17]

Simon Cassidy and John Henry, "Fatal toxicity of antidepressant drugs in overdose", *British Medical Journal*, vol 295, 14 October 1987, p.1021; Kapur, et al., "Antidepressant Medications and the Relative Risk of Suicide Attempt and Suicide", p.3441; Flanagan, "Fatal toxicity of drugs used in psychiatry", p.43.

13 R D T Farmer and R M Pinder, "Why Do Fatal Overdose Rates Vary Between Antidepressants?" *Acta Pscyhiatrica Scandinavica*, vol 80, October 1989, pp.31-34; Edwards, " Controversies on prevention, provocation, and selfpoisoning continue", p.207.

14 Cassidy and Henry, "Fatal toxicity of antidepressant drugs in overdose", p.1022; Farmer and Pinder, "Why Do Fatal Overdose Rates Vary Between Antidepressants?" pp.27-28; S A Montgomery, et al., "Why do amitriptyline and dothiepin appear to be so dangerous in overdose?" *Acta Pscyhiatrica Scandinavica*, vol 80, no 47 - 53, October 1989, p.52; O Morgan, et al., "Fatal toxicity of antidepressants in England and Wales, 1993-2002." *Health Statistics Quarterly*, vol 23, Autumn 2004, p.22; G W Kerr, et al., "Tricyclic antidepressant overdose: a review", *Emergency Medicine Journal*, vol 18, no 4, July 2001, p.236; Keith Hawton, et al., "Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose", *British Journal of Psychiatry*, vol 196, no 5, May 2010, pp.357-358.

15 N A Buckley, et al., "Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants", *The Lancet*, vol 343, 15 January 1994, p.161.

16 See Montgomery, et al., "Why do amitriptyline and dothiepin appear to be so dangerous in overdose?" p.52.

17 For an overview see MIMS Australia, "Prothiaden".

- **Dothiepin toxicity is a frequently occurring suicide method**

There is particular concern that Dothiepin poisoning features more frequently than other antidepressant poisoning in suicide deaths. An early study found that Dothiepin was one of the 12 drugs most frequently used for suicide by poisoning in the United Kingdom between 1975 and 1986.[18] More recently, it was identified as the antidepressant most commonly involved in British suicide deaths.[19]

Some researchers have proposed that the high frequency of suicide by Dothiepin poisoning is a result of Dothiepin being prescribed to more severely depressed patients who are at greater risk of suicide.[20] Another explanation put forward is that Dothiepin is highly toxic in overdose, so suicide attempts involving Dothiepin are more likely to end in death than suicide attempts involving other antidepressants.[21] This latter hypothesis is partially supported by a recent study which found that Dothiepin was the antidepressant most frequently involved in suicide deaths, but only sixth most frequent in terms of non-fatal poisonings.[22]

There is a particular suicide risk in the first month after commencing treatment with Dothiepin. This is because several weeks can elapse before significant remission of depressive symptoms occur, and in this time suicidal ideation and suicidal behaviour can emerge or worsen.[23]

- **Therapeutic and toxic levels of Dothiepin can be very close**

In the Victorian Institute of Forensic Medicine's (VIFM) standard General Comments Concerning Dothiepin, it is stated that:

> The usual therapeutic blood concentrations associated with Dothiepin use range up to ~ 0.5 mg/L when blood is taken from the femoral vein.

It is then further stated that:

> Fatalities associated with Dothiepin have had blood concentrations of 0.3 mg/L or higher.[24]

This suggests that therapeutic and fatally toxic blood concentrations of Dothiepin can actually overlap. However, it must be noted that other sources

18 P Crome, "The Toxicity of Drugs Used for Suicide", *Acta Psychiatrica Scandinavica*, vol 87, May 1993, p.33.

19 Hawton, et al., "Toxicity of antidepressants", p.355.

20 A number of studies reporting on completed and attempted suicides involving Dothiepin were reviewed in Thomas Keller, et al., "Fatal intoxication due to dothiepin", *Forensic Science International*, vol 109, 2000, p.164.

21 Adverse Drug Reactions Advisory Committee, "Warning for High Dose Tricyclic Antidepressants".

22 Hawton, et al., "Toxicity of antidepressants", p.355.

23 For a review of this risk see MIMS Australia, "Prothiaden".

24 These General Comments Concerning Dothiepin appear in most VIFM toxicology reports published since mid-2007.

state that Dothiepin blood concentrations associated with fatal toxicity are usually above 1 mg/L.[25]

A related issue with therapeutic and toxic levels concerns accumulation of Dothiepin in the body over time. As explained in the VIFM General Comments Concerning Dothiepin:

> Dothiepin has a long residence time in the body exceeding 1 day, and will on repeated daily dosing accumulate in the body. The use of high doses or the use of higher than recommended doses may result in the development of toxicity as a result of this accumulation.

Put another way, a therapeutic dose of Dothiepin can over time lead to potentially fatal Dothiepin toxicity.

- **Inter-individual susceptibility to Dothiepin toxicity varies**

For individuals taking a standard oral dose of Dothiepin, the maximum blood concentration of Dothiepin subsequently reached can vary dramatically.[26] Additionally, the blood concentration of Dothiepin required to induce a toxic effect varies between individuals based on differences in absorption, protein binding and metabolism.[27] As previously mentioned, fatal overdoses have occurred in individuals with a blood concentration as low as 0.3 mg/L; however there are reported instances where individuals have survived Dothiepin overdose with peak Dothiepin plasma concentrations varying from 0.8 to 4.7 mg/L.[28]

This means that knowledge of the amount of Dothiepin ingested by an individual does not provide an accurate guide to clinical outcomes (including toxic effects) the individual will experience. Additionally, postmortem levels of Dothiepin detected cannot be used as a direct indicator of drug contribution to the death; instead any postmortem findings must be interpreted by an experienced toxicologist.[29]

- **Dothiepin could be involved in deaths from heart conditions**

There are published reports that Dothiepin can cause myocardial infarction and ischemic heart disease;[30] this suggests that Dothiepin contribution might need to be considered when it is present in deaths from these causes.

(d) Dothiepin abuse and dependency

Evidence of Dothiepin abuse is not common in the literature; it does not produce the types of effects (such as euphoric effects) that are typical of

25 Keller, et al., "Fatal intoxication due to dothiepin", p.164.

26 MIMS Australia, "Prothiaden".

27 Kerr, et al., "Tricyclic antidepressant overdose: a review", p.236.

28 This point is made in VIFM's General Comments Concerning Dothiepin.

29 Keller, et al., "Fatal intoxication due to dothiepin", p.164.

30 Julia Hippisley-Cox, et al., "Antidepressants as risk factor for ischaemic heart disease: case control study in primary care", *British Medical Journal*, vol 323, 22 September 2001, p.666; Basant Arya, et al., "Myocardial infarction: a rare complication of dothiepin overdose", *International Journal of Cardiology*, vol 96, 2004, p.494.

abused drugs. However, the literature does suggest that abuse in some forms might occur.

First, there is a possibility that Dothiepin may be abused to induce mania, especially in bipolar patients with cluster B personality problems. Research indicates that Dothiepin should only be used to treat uni-polar depression because if used in individuals with bi-polar disorder, it may induce manic episodes. Caution regarding this possibility is warranted given that there is anecdotal evidence that some individuals misuse Dothiepin in order to trigger or prolong manic episodes.[31]

Second, there appears to be some evidence that Dothiepin is used by intravenous drug users in order to prolong and/or increase effects of heroin; TCAs have a potentiating effect on opiates. Studies in Dublin and Sydney found considerable populations of intravenous drug users who were misusing Dothiepin.[32] Amounts taken were up to 600mg daily (twice the maximum recommended dose). Individuals reported effects such as euphoria and sedation with complex visual and auditory hallucinations.

Third, while TCAs are not generally considered drugs of dependence,[33] there is a reported incident in the literature of consistently excessive Dothiepin consumption, followed by the temporal association of withdrawal symptoms with the cessation of this practice.[34] Withdrawal implies at least the potential for dependence and therefore abuse.

(e) Australian government regulation of Dothiepin

In Australia Dothiepin is a Schedule 4 controlled drug under the *Commonwealth Standard for the Uniform Scheduling of Medicines and Poisons*, which came into effect on 1 September, 2010. Schedule 4 controlled drugs are "substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription".[35]

Consequent upon this scheduling, Dothiepin must not be sold or supplied in Australia by a person other than a medical, dental or veterinary practitioner in the ordinary course of their professions or a pharmacist dispensing a legal prescription. A person who sells or supplies Dothiepin must keep it in a part of the premises which is not accessible by the public.

31 Peter Lepping and David Menkes, "Abuse of Dosulepin to Induce Mania", *Addiction*, vol 102, no 7, July 2007, p.1167.

32 Darke and Ross, "The use of antidepressants among injecting drug users in Sydney, Australia", p.408; Arthur Dorman and Dympna Talbot, "Letter to the Editor: Misuse of Dothiepin", *British Medical Journal*, vol 311, 2 December 1995, p.1502; S Hepburn, et al., "Deliberate Misuse Of Tricyclic Antidepressants By Intravenous Drug Users - Case Studies And Report", *Scottish Medical Journal*, vol 50, no 3, August 2005, pp.131-133.

33 Cheetham and Heal, "Antidepressant and anxiolytic drugs", p.516.

34 Gurvinder Pal Singh, et al., "Letter to the editor: Dothiepin dependence syndrome", *Indian Journal of Medical Sciences*, vol 58, no 6, pp.253-254.

35 See Department of Health and Ageing, Australian Government, *Standard for the Uniform Scheduling of Medicines and Poisons*, no 1, August 2010, p.76.

In Victoria, the *Drugs, Poisons and Controlled Substances Act* 1981 regulates the licences that authorise a person to manufacture, sell and supply (by wholesale) Schedule 4 controlled drugs including Dothiepin. It creates pecuniary penalties for forging, fraudulently altering or uttering (knowing that it has been forged or fraudulently altered) a prescription for Dothiepin. Pecuniary penalties also apply for obtaining Dothiepin by false representation.

(f) Guidelines for prescription

MIMS (a provider of independent medical information to Australian healthcare professionals) publishes the only Australian prescribing guidelines that explicitly and specifically address Dothiepin. There are two separate guidelines, for Dothep and Prothiaden, but the contents of each are practically identical.[36] Basic information includes the following:

- Dothiepin is for the treatment of major depression.
- Due to its toxicity in overdose and the slim margin between a therapeutic and toxic dose, Dothiepin should only be used in patients intolerant of or unresponsive to alternative treatment options for depression.
- The maximum daily dose should not exceed 200 mg.

The following contraindications are listed:

- Dothiepin should not be prescribed to treat depression or other psychiatric disorders in children and adolescents aged under 18 years.
- People who suffer epilepsy should not take Dothiepin, as it can lower the seizure threshold.
- Dothiepin should not be taken concomitantly or within 14 days of treatment with MAOIs, as the combination may cause cerebral excitation followed by coma and dangerous hyperthermia.
- Dothiepin should not be used during the acute recovery phase following myocardial infarction; it may produce conduction defects and arrhythmias.
- Dothiepin should not be used by those who have impaired liver or renal function.
- Dothiepin should not be used by people undergoing surgery, as it can interact with anaesthetics to increase the risk of arrhythmias and hypotension.

The following precautions are listed:

- Given that there is an increased risk of suicidal behaviour in the first weeks after Dothiepin treatment is commenced, patients should be monitored very closely during this time for signs of suicidality.

[36] The following material is drawn from MIMS Australia, "Prothiaden".

- Dothiepin should only be prescribed after the patient has been adequately screened to ensure that he or she is suffering depression rather than bipolar disorder.
- Latent schizophrenia may be activated by Dothiepin.
- Dothiepin decreases alertness, so it is best taken at night. Ability to drive or operate machinery might be affected.
- When treating suicidal patients, the smallest possible quantity of Dothiepin should be prescribed at one time, to limit the patient's ability to intentionally overdose on the drug.
- The prescribing medical practitioner must consider other medications the patient is taking, and assess the risk of drug interactions (see section 2.3.2 above).
- Care must be taken when Dothiepin is prescribed to people who suffer a number of conditions including cardiovascular disorders, hyperthyroidism, glaucoma, or impaired renal or hepatic function.
- A number of side effects have been observed in people using Dothiepin, including hypotension, changes in libido, nausea, vomiting, vision disturbance, drowsiness, dizziness, and urinary retention.
- Withdrawal of Dothiepin treatment should occur gradually in order to prevent a number of symptoms including headaches, nausea, convulsions, and thrombotic episodes.

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has published clinical guidelines for the treatment of depression.[37] These do not address Dothiepin specifically, but set out a number of general principles for prescribing TCAs and other antidepressants. The RANZCP guidelines are quite detailed and as such difficult to summarise, but they include the following prescription principles that are of relevance to this report:

- The approach to treating depression is determined by the type of depression (mild, moderate, severe, melancholic, atypical or psychotic).
- Mild depression can be treated through supportive clinical care in the absence of medication, but treatment for the other types of depression invariably involves medication.
- If a first line (or initial) treatment for depression using a medication does not produce an adequate positive effect, the medication dose should be reviewed and consideration given to switching medications.

[37] Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, "Australian and New Zealand clinical practice guidelines for the treatment of depression", *Australian and New Zealand Journal of Psychiatry*, vol 38, no 6, June 2004, pp.389-407.

There is a Therapeutic Guideline for TCA use and prescription in Australia.[38] Like the RANZCP guidelines, the Therapeutic Guideline is very general in nature; it covers all TCAs rather than Dothiepin alone. It indicates, inter alia, that:

- TCAs are not appropriate for the treatment of depression in children under 16 years of age.
- Older people prescribed TCAs need to be monitored closely because they are particularly susceptible to the drug's toxic side effects.
- TCAs should only be used with caution in patients with epilepsy.

The USA-based DynaMed organisation also provides general guidelines for TCA use, in the form of a clinical reference tool.[39] This tool contributes the following additional information of relevance to Dothiepin:

- Suicide, cardiac arrhythmias and sedation are major risks that should be monitored when using a TCA.
- A number of checks should be made before prescribing a TCA. The suggested checklist includes blood pressure, liver function, glaucoma testing, suicide assessment, an assessment of possible interactions with other prescribed drugs, urinary obstructive symptoms, and prostate size in men.
- It is cautioned that TCAs have been associated with an increased risk of sudden cardiac arrest and that there are a number of cardiovascular side effects of taking TCAs.
- Other side effects that need to be monitored include anticholinergic side effects (including blurred vision, constipation, psychosis, delirium), neurological side effects (including sedation, disturbed sleep, analgesia), metabolic side effects (including weight gain and fluctuation in blood sugar levels), and other side effects including nausea, hepatitis and sexual dysfunction.

(g) Consumer information

Alphapharm Pty Limited (manufacturers of Dothep) and Abbott Australasia Pty Ltd (manufacturers of Prothiaden) produce consumer information leaflets for Dothiepin.[40] Both leaflets contain the following common advice:

- Dothiepin should not be taken if an individual has epilepsy, has recently had a heart attack or has liver failure.
- Dothiepin should not be taken concurrently with any MAOI, nor should it be taken within 14 days of having taken any MAOI. This is because it may cause a serious reaction, including sudden increase in body temperature, extremely high body temperature and severe convulsions.

38 Therapeutic Guidelines Limited (eTG Complete), "Tricyclic antidepressants", October 2008.

39 DynaMed, "Tricyclic antidepressants (TCAs)", 14 June 2010.

40 Alphapharm Pty Limited, "Dothep: Consumer Medicine Information", 6 May 2008; Abbott Australasia Pty Ltd, "Prothiaden: Consumer Medicine Information", 14 November 2007.

- The use of Dothiepin should be discussed with a GP if an individual is pregnant or breastfeeding.
- The patient should notify the prescribing doctor if he or she has heart or blood vessel problems, liver or kidney problems, glaucoma, prostate problems, difficulty in passing urine, thyroid problems, or a number of other medical conditions.
- The patient should notify the prescribing doctor if he or she experiences mental illness including particularly schizophrenia or manic depression, or a family history of suicide or manic depression.

The consumer information for Dothep and Prothiaden differ in the following ways:

- The Dothep leaflet contains an indication that the 75mg tablets "are only approved for the maintenance treatment of depression". There is no such indication on the Prothiaden leaflet
- The Dothep leaflet contains a note that "Dothep is not approved for use in children and adolescents below 18 years of age for the treatment of depression". Again, there is no such note on the Prothiaden leaflet. However, the Prothiaden leaflet mentions that "families and caregivers of children and adolescents being treated with Prothiaden need to monitor these patients for the emergence of a number of symptoms".
- The maximum daily dose for Dothep is 200 mg per day. There is no information on maximum daily dose for Prothiaden; instead the Prothiaden consumer information leaflet states that "the dose varies from patient to patient and will be adjusted by your doctor according to your response to treatment".

The following additional material contained in the consumer information leaflets is notable:

- The Prothiaden leaflet notes that "[the consumer's] doctor may have prescribed the medication for reasons other than for the treatment of depression".

Appropriateness of medical care for PC

(a) The diagnosis of depression

A diagnosis of depression appears to have been originally made by P's general practitioner Dr Jennifer Sanders in October 2005. This diagnosis was supported by the consultant psychiatrist Dr Chris Percival, who saw P in May 2008; Dr Percival added that P's illicit drug use was "almost certainly" for the purpose of self-medicating the depression.

It appears that in September 2008, on the last occasion when Dr Percival saw P, he expressed some doubt as to whether P actually had a "potentially treatable depressive illness," though he did not venture any other diagnosis. In January 2009 Dr Sanders raised a more concrete concern as to the adequacy of the diagnosis of depression, noting that P was exhibiting paranoid behaviour. Dr Sanders made multiple attempts to refer P to psychiatrists and psychologists, but none of these had come to fruition by the time P died a month later.

Psychiatrist Dr Carl Timothy Golumbeck noted in his expert opinion dated 17 March 2010 the probability that in the lead-up to P's death he had a prodrome[41] of a serious mental illness that was complicated and possibly masked by ongoing substance abuse. In particular, a review of the medical notes and statements reveals that P was clearly experiencing symptoms such as auditory hallucinations and paranoid beliefs about strangers that would indicate the onset of serious mental illness. It is possible that P's substance abuse proximal to his death was an attempt to self-medicate these symptoms, as was the excessive consumption of Dothiepin that led to his death.

It is unfortunate that P was unable to be successfully referred to a psychiatrist after Dr Sanders identified his paranoid behaviour. The outcome of a successful referral could only be guessed at, but it would be hoped that the psychiatrist might have detected the prodrome and instituted effective treatment including a review of the appropriateness of treatment with Dothiepin.

(b) Treatment with Dothiepin

When Dr Sanders diagnosed depression in October 2005 she commenced P on the SSRI Fluoxetine at 20 mg per day, and in July 2006 increased the dose to 40 mg per day. Following what appear to be concerns over whether the Fluoxetine was effective, Dr Sanders then switched P to the SNRI Venlafaxine in December 2006. P subsequently expressed concern that the Venlafaxine was negatively affecting him. On 2 July 2008 Dr Sanders commenced P on 75 mg Dothiepin per day at the instruction of Dr Percival. On 9 July this dose was abruptly increased to 300 mg per day, also at the instruction of Dr Percival because it appeared that the lower dose was not working. P continued to be prescribed 300 mg Dothiepin per day through to his death.

[41] In clinical medicine, a prodrome refers to the early symptoms and signs of an illness that precede the characteristic manifestations of the acute, fully developed illness.

The initial prescribing of Dothiepin appears to have been in line with the MIMS guidelines and the RANZCP guidelines. Specifically, an SSRI and an SNRI were tried as first line treatment options, were ceased due to side effects, and only then was Dothiepin introduced as a treatment.

However, the four-fold increase in Dothiepin dosage from 75 mg to 300 mg daily only a week after initial prescription does not appear to be congruent with either set of guidelines. The RANZCP guidelines state that a change in dose is an option to consider if the current treatment is not producing an adequate response,[42] but there is no evidence of inadequate response for P.[43] The MIMS guidelines state that the maximum recommended daily dose of Dothiepin is 200 mg,[44] well below the 300 mg level established here.

A further concern is raised by the contents of a letter Dr Percival sent to Dr Sanders dated 4 September 2008 concerning P's treatment, in which he concluded:

> In the circumstances therefore there is little more that can be done, with the probability of an ongoing exploration of the potential benefits of all of the available anti-depressants seeming unlikely to be particularly successful. However, should you feel so inclined, it would be not entirely unreasonable to cycle through the available alternatives, starting with a modest, but not unreasonably low, dose, and then titrating upwards in search of an adequate clinical response in the absence of any significant side effects.

This suggests that the very high Dothiepin dose was not achieving its desired clinical outcome and alternative treatments should have been considered. If this is the case, the question arises as to why P was continued on this high dose for another five months. Further to this point, Dr Sanders records in her statement dated 20 June 2009 that Dr Percival "was worried about the risk of P overdosing" from the 300 mg daily dose of Dothiepin; this should have been a further impetus to change the treatment regime when its suitability fell into doubt.

From Dr Percival's perspective, the question of why P remained on the 300 mg daily dose of Dothiepin would be presumably none of his concern; he made clear in the 4 September 2008 letter that he was terminating his therapeutic relationship with P and handing all decisions on treatment back to Dr Sanders. Dr Sanders' explanation for continuing P on the 300 mg of Dothiepin daily was that she didn't want to change his treatment regime until he had seen a new psychiatrist. She gave evidence that as a general practitioner, she would not normally prescribe Dothiepin in that dose or that quantity, however, psychiatrists often prescribe over the recommended dose of medications.

[42] Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, "Australian and New Zealand clinical practice guidelines for the treatment of depression", p.393.

[43] Further to this point, given that TCAs can take some weeks before their antidepressant effects are asserted, there is a question as to whether a week would be enough time to establish inadequate response.

[44] MIMS Australia, "Prothiaden".

P was put on the high Dothiepin dose by Dr Percival, and was then effectively 'stuck' on this dose when Dr Percival terminated the therapeutic relationship and the general practitioner, Dr Sanders, was unable to secure further expert psychiatric guidance. A successful referral might have led to a review of the appropriateness of the high Dothiepin dose.

A final concern is the amount of Dothiepin tablets per prescription that P could obtain. In July 2008 when Dr Percival increased P's Dothiepin dose to 300 mg daily, he apparently instructed the chemist not to dispense more than a week's worth of tablets to P at a time, to reduce the risk that P would overdose.[45] P's mother MC corroborates this instruction in her statement dated 24 April 2009, recalling that "when [P] was first prescribed [Dothiepin] he was only allowed to have one box a week and he collected them weekly". However at some stage this arrangement changed such that a month's worth of Dothiepin tablets could be collected at once. It is not clear when this changed or why. Nor is it clear that remaining on the weekly dispensing regime could have prevented P's death. But in any event the concern should at least be documented that P was being given access to very large amounts of Dothiepin at a single time in the lead-up to his death.

(c) Dual diagnosis

Dr Percival wrote in his statement to police dated 16 June 2009, that:

> Essentially the insurmountable difficulty in treating youngsters like P on an outpatient basis is that their inability to refrain from the consumption of illicit drugs renders diagnosis almost impossible, and therefore any rational approach to treatment equally impossible.
>
> Sadly, even if the appropriate facilities were available, which in general they are not, management on an inpatient basis, whilst in my view highly desirable, is usually equally impossible as the patients will not accept this on a voluntary basis, and are not ill enough to qualify for compulsory admission under the Mental Health Act.

When an individual experiences both a mental health and a substance use disorder, the disorders tend to influence each other in their development, their severity, their response to treatment and their relapse circumstances.[46]

Dr Percival's claim that it is "almost impossible" to diagnose or treat such patients is not in keeping with medical practice. The dual diagnosis

[45] In Dr Sanders' statement dated 20 June 2009 she writes that Dr Percival "was worried about the risk of P overdosing and had informed the chemist to not provide more than one weeks worth of tablets at the time". However there is no statement from the chemist confirming this.

[46] Katherine L Mills, et al., *Guidelines on the management of co-occurring alcohol and other drug and mental health conditions in alcohol and other drug treatment settings*, National Drug and Alcohol Research Centre, University of New South Wales, 2009, pp.9-12; Maree Teesson and Heather Proudfoot, "Responding to comorbid mental disorders and substance use disorders", in *Comorbid mental disorders and substance use disorders: Epidemiology, prevention and treatment*, Edited by Teesson and Proudfoot, Canberra: Australian Government Department of Health and Ageing, 2003, pp.1-9.

approach to care is well established, and there are a number of specialist dual diagnosis services available across Victoria including the Western Hume Dual Diagnosis Service,[47] which covers the Shepparton region where P resided.

Dr Percival identified that dual diagnosis was a serious issue, but neither he nor any other medical practitioner appears to have considered a dual diagnosis approach to P's care.

Summary of findings

- Dothiepin is highly toxic relative to other antidepressants. In particular, the ratio of fatal to non-fatal poisonings is higher for Dothiepin than other antidepressants, as is the rate of fatal poisonings per million prescriptions.
- Dothiepin can interact with other drugs to produce toxic effects. These effects have been observed when Dothiepin is combined with drugs including alcohol, barbiturates, central nervous system depressants, anti-epileptics, anticholinergics and antidepressants (particularly MAOIs and other TCAs).
- Dothiepin is used in suicides more frequently than other antidepressants. This may be because of its inherent toxicity, or because it is prescribed to patients at greater risk of suicide (it is often used as a 'drug of last resort' for patients whose depression is resistant to other treatments).
- Fatally toxic levels of Dothiepin have been recorded that are very close to therapeutic levels. There is a risk of unintentional poisoning when using Dothiepin as directed.
- Dothiepin can cause problems (sometimes fatal) for people suffering a variety of health issues including cardiovascular disorders, hyperthyroidism, glaucoma, and impaired renal or hepatic function.
- For all these reasons, Dothiepin is not recommended as a first line treatment for depression. Instead it should be prescribed only when other options have been exhausted. A patient prescribed Dothiepin must be thoroughly assessed for known precautions and contraindications, and must be closely monitored during treatment for signs of suicidality, toxicity, and so on.
- In the lead-up to P's death he may have been suffering from an unidentified prodrome of a serious mental illness.
- P continued to be treated with 300 mg of Dothiepin daily (well in excess of the recommended amount) for several months after it was apparent that this treatment was not working.
- P was not treated using a dual diagnosis approach to his substance abuse and mental illness.

[47] The telephone number for the Western Hume Dual Diagnosis Service is 03 5832 2100.

- After P's clinical relationship with Dr Percival deteriorated, Dr Sanders was unable to secure the services of another psychiatrist to see P and review his treatment.

Recommendations

There were several missed opportunities that might have led to P's death being prevented. For example if P had been treated using a dual diagnosis approach (rather than his substance abuse being viewed as a 'nuisance' factor that inhibited identification and treatment of his mental health issues) then this might have had a positive impact. If he had been successfully referred to another psychiatrist after the therapeutic relationship with Dr Percival broke down, his prodrome might have been identified and his Dothiepin treatment regime changed. If he had not been prescribed such a large daily Dothiepin dose that was dispensed in such large amounts, toxicity may have been avoided

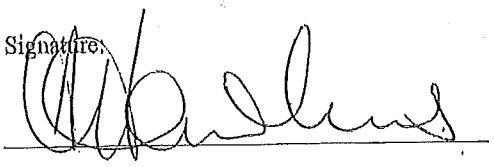
At the very least, a dual diagnosis approach should have been taken and it is reasonable to state that the high-dose Dothiepin treatment should have been reviewed after it became obvious that it was not working as hoped.

Conclusion

From the evidence available it is impossible to determine that P intended to take his own life. His death is more likely to have been caused by a cumulative toxicity of Dothiepin.

On the basis of the timeframe between his medication being dispensed and his death, it is reasonable to presume that P consumed 30 Dothiepin 75 mg tablets in a 48-hour period. This would almost certainly be a fatal dose.

Signature:



Date: 07/02/2011