

Psychiatrist, Dr A
Southern District Health Board

A Report by the
Health and Disability Commissioner

(Case 11HDC01072)



Health and Disability Commissioner
Te Toihau Hauora, Hauātanga

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Executive summary

Background

1. In 2010 and 2011, Psychiatrist Dr A treated 11 patients on Ward X at a public hospital with intramuscular injections of ketamine. Each patient had treatment-resistant depression (TRD). Dr A is employed by a university and holds a clinical position with the Southern District Health Board.
2. Ketamine is only approved for use in New Zealand as an anaesthetic. The unapproved use of an approved medicine is termed “off label” and is subject to practice guidelines.
3. Six patients were prescribed ketamine between 19 April 2010 and 13 September 2010. The clinical notes document that there was a discussion with each patient about the use of ketamine, and the patients gave verbal consent to the treatment. Those six patients did not provide written consent to the treatment. All patients received written information about ketamine.
4. On 20 September 2010 an information/consent sheet on the use of ketamine in treating depression was created. The five patients who were subsequently treated with ketamine for TRD signed that information/consent sheet. The information/consent sheet was modified in April 2011 to include a sentence to the effect that the use of ketamine in this way was off label.
5. No individual patient has complained about either the informed consent process or the provision of ketamine. However, the Code of Health and Disability Services Consumers’ Rights (the Code) requires informed consent in writing if the consumer is to participate in research or if the procedure is experimental.
6. My consideration of this matter centred on three key issues:
 - Was the prescription of ketamine clinical research?
 - If it was not research, could the prescription of ketamine be categorised as an experimental procedure?
 - Were the relevant practice guidelines complied with when prescribing ketamine off label?

Findings

7. It is important that innovation is able to flourish in the health and disability sectors. However, it is even more important that consumers are fully engaged in their treatment and fully informed as to their options and choices, and that they properly consent to their treatment course.
8. I accept that the patients involved in this case were provided with the information they needed, and that the decisions they made were made on an informed basis.

Dr A — adverse comment

9. The controversy surrounding these events demonstrates that different minds may form different views as to whether or not a particular treatment amounts to research, or is experimental. Dr A formed the view that the extant research provided a sufficient base on which to treat patients with ketamine. I accept that this position was not unreasonable, and was thus open to Dr A.
10. Dr A's research interests in this area undoubtedly informed his use of ketamine in Ward X. There is nothing unusual or inappropriate in that. However, these interests were generally known, and thus it was not beyond the realms of possibility that his treatment of patients in Ward X with ketamine would raise questions as to whether or not research was being undertaken.
11. While it would go too far to suggest there was ambiguity in Dr A's actions, there was insufficient formality in relation to what was clearly an uncommon approach to treatment of patients with TRD. Aspects of the record-keeping processes adopted should have been better. I am satisfied that the evidence does not, on the balance of probabilities, support a finding that research was being undertaken. I am also satisfied that the evidence does not, on the balance of probabilities, support a finding that the treatment, although uncommon, was experimental.
12. I accept that overall Dr A complied with the Royal Australian and New Zealand College of Psychiatrists Practice Guidelines when prescribing ketamine to the patients in Ward X. However, a more explicit discussion of the fact that this was off-label prescribing, and the anticipated end point of the treatment, and careful recording of that discussion, should have occurred for all patients.
13. My expectation is that in the future Dr A and his colleagues will adopt a more disciplined approach to the recording of consultations with peers when approaching the question of whether a treatment is experimental and whether it also constitutes research.

Southern District Health Board — adverse comment

14. In April 2010 there was no requirement that Dr A advise the DHB of his intention to prescribe this off-label medication. I am of the view that the DHB should have had in place a requirement that management be informed about the proposed prescribing of medication in a manner not previously known to have been prescribed in New Zealand. In my view, it was suboptimal for Southern DHB to adopt a "hands off" system of oversight.
15. In contrast to a number of other DHBs at the time of these events, Southern DHB did not have a policy in place regarding off-label prescribing. The policy that has subsequently been developed by Southern DHB requires that when prescribing an approved medicine for an unapproved indication in the absence of evidence from "well conducted clinical trials", the SMO must consult with at least one other SMO colleague and document the outcome in the patient record, and obtain written patient consent. I note that there are differing opinions as to what amounts to evidence from "well conducted clinical trials", and it is unclear what the requirement imposed by the

policy means in practice. In addition, the point at which the concurrence from peer consultation is sufficiently positive is uncertain. I do not consider that the policy developed by the DHB is sufficiently specific to make the DHB's expectations clear, such as, for example, the circumstances in which peer review is required. Accordingly, I recommend that the DHB review the policy.

16. I have made recommendations with regard to Dr A, Southern DHB, all New Zealand DHBs, and the National Health Board.

Complaint and investigation

17. The Health and Disability Commissioner (HDC) received a referral from the National Health Board, following which, HDC commenced a Commissioner Initiated Investigation pursuant to section 40 of the Health and Disability Commissioner Act 1994 (the Act).

18. The scope of the investigation was:

- *The appropriateness of services provided by Southern DHB to patients receiving ketamine on Ward X, the public hospital, in 2010 and 2011.*
- *The adequacy of the information provided by Southern DHB to patients receiving ketamine on Ward X, the public hospital, including the informed consent process.*
- *The appropriateness of the services provided by Dr A to patients receiving ketamine on Ward X, the public hospital, in 2010 and 2011.*
- *The adequacy of the information provided by Dr A to patients receiving ketamine on Ward X, the public hospital, including the informed consent process.*

19. Information was obtained from:

Dr A	Provider
Southern District Health Board	Provider
Mr B	Consumer Advocate
Mr C	Consumer Advisor
Dr D	Psychiatrist, Southern DHB
Dr E	Consultant Psychiatrist, Southern DHB
Dr F	Consultant Psychiatrist, Southern DHB
Dr G	Psychiatry Registrar, Southern DHB
Dr H	Consultant Psychiatrist, Southern DHB
Dr I	Psychiatry Registrar, Southern DHB
Dr J	Former Trainee Intern
Dr K	Former Trainee Intern
Dr L	Former Trainee Intern
RN M	Registered Nurse

RN N	Registered Nurse
Ms O	Community Mental Health Nurse
Patient 1	Consumer
Patient 2	Consumer
Patient 3	Consumer
Patient 4	Consumer
Patient 5	Consumer
Patient 6	Consumer
Patient 7	Consumer

Also mentioned in this report:

Dr P	Consultant psychiatrist
Dr Q	Consultant psychiatrist
Mr R	Academic psychiatrist
Patient 8	Consumer
Patient 9	Consumer
Patient 10	Consumer
Patient 11	Consumer
Mr S	Consumer

20. Independent expert advice was obtained from Specialist Adult General Psychiatrist Dr Allen Fraser and is set out in **Appendix A**.
21. Independent expert advice was also obtained from Psychiatrist Associate Professor (Sylvester) Wayne Miles and is set out in **Appendix B**.
22. This report is the opinion of Health and Disability Commissioner Anthony Hill.

Information gathered during investigation

Background

Dr A

23. Dr A is a psychiatrist with qualifications in clinical psychopharmacology. He is employed by a university. He also holds a clinical position with Southern District Health Board (the DHB) under a joint academic-clinical agreement between the university and the DHB. The DHB reimburses the university the portion of the remuneration and other employment-related costs associated with the clinical component of his role. While performing duties for the DHB, Dr A is bound by the policies and procedures of the DHB.
24. Dr A's research focuses on clinical and basic science. His areas of interest include the pharmacology of drug treatments in psychiatry, and the investigation of disease mechanisms in neurological and psychiatric disorders. He is also interested in technical aspects of clinical trial design, including trialling simulation and modelling. He has published extensively.

Ketamine

25. Ketamine was first developed in 1962, and in 1966 it was patented as an anaesthetic for humans and animals. It is a drug widely used in human and veterinary medicine, primarily for the induction and maintenance of general anaesthesia, usually in combination with a sedative. Other uses include sedation in intensive care, analgesia (particularly in emergency medicine), and treatment of bronchospasm.
26. Ketamine has a wide range of effects in humans, including analgesia, anaesthesia, hallucinations, elevated blood pressure, and bronchodilation. It induces a state referred to as “dissociative anaesthesia” and is used as a recreational drug.
27. The hydrochloride salt of ketamine is sold as Ketanest, Ketaset, and Ketalar. The Ketalar data sheet states that “[i]t is formulated as an acid (pH 3.5 to 5.5) solution for intravenous or intramuscular injection”. The data sheet notes that ketamine has been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies, and that adverse reactions have occurred in approximately 12% of patients.
28. Ketamine is approved by Medsafe for use in New Zealand as an anaesthetic agent only.

Medicine approval and “off-label” use

29. Companies wishing to sell a medicine in New Zealand must make an application to Medsafe for approval. Medsafe then reviews the application, including information about the quality, safety and efficacy of the medicine concerned, and makes a recommendation to the Minister of Health as to whether the medicine should be approved.¹
30. Medicines are approved for particular indications, dosages and routes of administration, as specified on the approved New Zealand data sheet. Approved medicines may legally be used in ways other than as specified on the data sheet, a practice that is termed “off-label” use. In some areas of medicine (such as paediatrics), clinical trials are seldom conducted. Lack of evidence from clinical trials means that approval is generally not sought for the use of medicines in those patient populations. Consequently, medicines are commonly used off label in those areas.
31. Medsafe’s statement entitled “Use of Unapproved Medicines and Unapproved Uses of Medicines” (reviewed by Medsafe in April 2012) states:

“For an unapproved medicine or unapproved use, the consumer should be advised of the unapproved status. The consumer should also be advised of the degree and standard of the support for the use of the medicine, and of any safety concerns, or warnings or contraindications regarding its use in their particular condition.”

¹ Medsafe, “Information for Consumers: Quality and Safety of Medicines: Medsafe’s Evaluation & Approval Process” www.medsafe.govt.nz, accessed 3 April 2013.

Ketamine and treatment-resistant depression

32. Treatment-resistant depression (TRD) or treatment-refractory depression is a term used in clinical psychiatry to describe cases of major depressive disorder that do not respond to adequate courses of at least two antidepressants.² TRD is associated with suicide attempts and increased mortality.³ A study in the United Kingdom observed that the average decrease in life expectancy for patients with recurrent major depressive disorder is 7 years lost for females and almost 11 years lost for males.⁴
33. Ketamine is not approved in New Zealand for the treatment of depression. Therefore, the use of ketamine for that purpose is an off-label use of the medicine.
34. HDC has been provided with no evidence that, prior to 2010, ketamine had been prescribed for TRD in any clinical or research setting in New Zealand.

Prior enquiries into the use of ketamine on Ward X

Complaint received

35. On 3 December 2010, a complaint was made to HDC by Mr B regarding the use of ketamine on Ward X at the public hospital. Mr B made his complaint as a third party complainant, rather than as a consumer or on behalf of any particular consumer. The complaint was not supported by any consumer who had received ketamine treatment.

Earlier HDC enquiries

36. On 9 February 2011, HDC requested information from Dr A including specific comments on whether he was conducting clinical research on the use of ketamine as a treatment, whether Ethics Committee approval had been obtained, and whether patients had given their informed consent to “off-label” use of ketamine.
37. On 4 March 2011, the DHB advised that the use of ketamine on Ward X was not clinical research or a clinical trial. The DHB stated that it was off-label therapeutic prescribing to patients with severe TRD, who had given informed consent. The DHB stated: “[Dr A] notes that there is substantial published scientific literature on this use in treatment resistant depression.”
38. The DHB said that “patients were carefully assessed clinically to ensure there were no medical or psychological reasons that might impair their ability to provide informed consent (e.g. presence of intoxication, delirium, intellectual disability). No patients under the Mental Health Act were considered for consent.”
39. HDC asked what information was provided to patients when obtaining their informed consent, specifically, whether the patients were informed that ketamine was being prescribed “off label”, and the risks involved in “off-label” use. The DHB advised that the following items of information were “available” initially:

² Wijeratne, C and Sachdev, P, “Treatment-resistant depression: critique of current approaches”, *The Australian and New Zealand Journal of Psychiatry* (2008) 42 (9): 751–62.

³ Onlin B et al, “Mortality and suicide risk in treatment resistant depression-: An observational study of the long term impacts of intervention” (2102) PLoS ONE 7(10).

⁴ Chang C-K et al, “Life Expectancy at Birth for People with Serious Mental Illness and Other Major Disorders from a Secondary Mental Health Care Case Register in London” (2011) PLoS ONE 6(5).

- The Ketalar data sheet.
 - A copy of a published research study (Zarate 2006⁵).
40. The DHB stated that subsequently a second research publication was also “available” (Diazgranados 2010⁶) along with a patient information sheet that mentioned approved uses of, and risks associated with the use of, ketamine. However, the documentation of the information provided is variable, particularly with regard to those patients who gave verbal consent. HDC considered the word “available” to be ambiguous and so further requested the DHB to confirm whether the ketamine product information sheet, published research papers, and the Ketamine Consent Form were provided to consumers before their consent was obtained to be treated with “off-label” ketamine.
41. The DHB responded:
- “The Ketalar information sheet and Zarate paper were given to patients from April 2010. The Diazgranados 2010 paper was also given to patients from August 2010. Because of the technical nature of these documents, an information sheet and consent form was made available from September 2010, with the more detailed documents available if patients had questions. All patients treated with ketamine received written information.”⁷
42. On 15 April 2011 HDC advised Dr A and the DHB that no further action was being taken on the complaint pursuant to section 38(1) of the Health and Disability Commissioner Act 1994 (the Act). However, the letter noted that the patient information/consent sheet did not specifically mention that ketamine was being used “off label”, and what “off-label” use means. HDC advised that it would be appropriate for such information to be included for consumers as part of the informed consent process. Later that month, the information/consent sheet was modified to include that the ketamine use was “off label”.
43. The information/consent sheet was dated 20 September 2010. On 24 May 2011, Mr B requested that the Commissioner revise his decision to take no further action and raised a number of additional concerns. In particular, he alleged that the information/consent sheet was incorrectly dated September 2010 and that, as at 27 January 2011, the information/consent sheet was not available to consumers.
44. In response, the DHB advised that ketamine was first used as a treatment for depression for patients on Ward X on 19 April 2010, and that 11 patients had been treated off label with ketamine. Patients who received treatment after 24 January 2011 signed the information/consent sheet. In total, five patients had given written consent

⁵ Zarate, CA Jnr et al, “A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression” (2006) *Arch Gen Psychiatry* 63(8) 856–64. This was a randomised, placebo controlled, double-blind, crossover study involving 17 subjects.

⁶ Diazgranados, N et al, “A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression” (2010) *Arch Gen Psychiatry* 67(8) 793–802. This was a randomised, placebo controlled, double-blind, crossover study involving 18 subjects.

⁷ See **Appendix C** for detail of the information provided to each patient.

to receiving ketamine, while six patients had given verbal consent to have the treatment after having had information about ketamine provided by medical staff.

National Health Board enquiries

45. Between May 2011 and August 2011, the National Health Board carried out an assessment of systems and processes at the public hospital in conjunction with the DHB. The report was finalised on 12 August 2011. The National Health Board advised that during that assessment, processes and systems around the use of ketamine in the mental health service at the public hospital were identified as requiring further examination. An assessment of the use of ketamine was subsequently conducted by a team of four assessors.
46. The assessment team considered that the DHB did not “thoroughly investigate” the 2010 complaint before responding to HDC and failed to provide all the facts. On 4 October 2011 the National Health Board referred the matter to HDC, stating that the questions needing to be answered were:
 - “• Was it appropriate for ketamine to be offered as an ‘off-label’ treatment for depression in mental health patients in 2010?
 - Was ketamine offered as an experimental treatment and/or being offered as part of a research study for patients with depression in the mental health service?
 - Were adequate informed consent processes implemented for the use of ketamine in the mental health service in 2010?
 - Did [Dr A] act professionally and ethically?
 - Did the DHB mislead the HDC via the information provided in response to HDC questions?
 - Are changes required by the DHB in how they manage ‘off-label’ treatment and research and what would those changes be?
 - Did the DHB manage the complaint appropriately?”
47. After careful consideration of all the information before him, the Commissioner commenced this Commissioner Initiated Investigation pursuant to section 40 of the Act.

Treatment provided

48. A table of the patients who received ketamine, the consent processes, and the number of treatments is set out in **Appendix C**.

Interviews with DHB staff

Dr A

Staff discussions

49. Dr A advised that he had discussions with the ward team, including the senior nurses and junior doctors, about the use of ketamine and how it was to be administered, and the safety assessments, mood assessments, and so on. He stated that he did not discuss these matters with medical colleagues who were general psychiatrists because none of them had the same awareness of the literature. In addition, when he made an application for funding in 2008 to research dose responses, the feedback indicated to him that this was a clinical management problem rather than a scientific issue.

Peer review

50. Dr A advised that he undertakes weekly peer review with three or four other psychiatrists regarding acute inpatient psychiatry. The peer review covers a number of different topics, most commonly patient management. He advised that the group discussed “certain aspects around patients responding to ketamine, not responding to ketamine”.
51. He stated: “I remember [Dr P] bringing along a number of different references on the specific effect of [ketamine with regard to] suicidality to one of the meetings and he used that as a basis for discussion. [Dr E] was another member who also treated two or three patients with Ketamine.” Dr A advised that there were “not really any divergent opinions” in the group about ketamine use.

Patient selection for ketamine treatment

52. Dr A advised that all of the patients who received ketamine treatment had been assessed as suffering from TRD. He advised that factors considered in deciding whether a person has TRD include the duration of the depression, the level of symptom severity, how many treatment failures the person has had, whether augmentation had been tried, and whether ECT had been tried.
53. Dr A advised that he used standard approaches to assess patients’ suitability for treatment with ketamine — patients were interviewed, they had a full assessment including a mental state examination, their past history and notes were reviewed, and the treatments they had had in the past and their responses to the treatments were considered.
54. Dr A advised that the first patient he treated with ketamine for TRD was Patient 1 (see **Appendix C**) who, in his view, was very sick and nothing else was alleviating her symptoms. He said that her ketamine treatment was very successful, and she has not been readmitted to hospital and has been keeping well.
55. Dr A advised that there are no treatments for TRD that have been approved by Medsafe.

Consent

56. Dr A advised that he always conducted the verbal consent process personally, although there would invariably be other people in the room with him. With regard to

the consent process undertaken with Patient 1, Dr A advised that he gave her the Zarate article and the Ketalar information sheet and talked her through the information. Dr A stated:

“I think I talked about being off-label, that this wasn’t an approved use, and, you know, it’s again, in terms of off-label, you know, that no company has applied for a license from Medsafe to be able to use a medication in this way. I’m not sure I particularly used those terms.”

57. Dr A advised that the consent related to a single dose of ketamine, and he did not give Patient 1 information about IV administration versus IM administration, because the information would be technical. Additionally, he said that if a patient required further treatments, it would not be usual to obtain additional consent before each treatment.
58. Dr A advised that the information/consent sheet was prepared in September 2010. He developed the sheet because at that time he was developing a study to consider whether ketamine worked in severe depression associated with terminal cancer. As part of the ethics proposal for Ethics Committee approval, he prepared an information sheet and a consent form, and he decided to use the information/consent sheet for patients who were being treated with ketamine on Ward X.
59. He stated that the information/consent sheet was not used between September 2010 and January 2011 because no patients were treated with ketamine in that period, as no suitable patients presented in Ward X.
60. In April 2011, the information/consent sheet was amended because of a suggestion from HDC that patients should be informed that ketamine was being used “off label”. In September 2011, HDC further pointed out that the information/consent sheet did not explain what “off label” means, and so that was added into the current version.

Research?

61. Dr A advised that he was not planning to write up the results of the ketamine treatment in 2010/2011 and said:

“No, it was really that we had these incredibly sick patients with no real options and it was more with the results with [Patient 1] and [Patient 7] that there was actually an important point here that if you look at this and say, in terms of clinical audit ... this is an important finding that might, you know, help other doctors who are dealing with similar patients.”
62. Dr A advised that, in his opinion, research is hypothesis driven. It has specific protocols and endpoints. He said that he perceived the use of ketamine and the collection of any data as “falling into clinical audit”.
63. Dr A stated: “Clearly when you are starting to randomise patients with an 80% placebo I think that is quite a different situation from when you are dealing with ... an unselected individual patient in a ward setting.”

64. When asked whether he intended to compare the patients in Ward X with those receiving conventional treatment or other treatments, Dr A advised that the patients were well spaced with 11 or so patients over a year and, in addition, the patients had different conditions. Some had bi-polar depression and some had uni-polar depression. Others had concurrent medical disorders, such as HIV, and some had personality disorders. Dr A stated:

“This is a very heterogeneous group of patients and their pathways to treatment resistant depression are different. Some might have eight antidepressants fail, some might have six, perhaps a couple of mood stabilisers. If one were to do the full experiment and say, well who would I compare these people with, you know, there is no obvious control group.”

65. When asked whether he was testing a hypothesis in treating patients with TRD with ketamine, Dr A responded: “I guess if you want to look at it in hypothesis terms, it’s ‘can we make them better?’”
66. Dr A obtained a report from a consultant psychiatrist/researcher which he submitted to HDC. The consultant psychiatrist/researcher opined:

“It is clear from the state of the literature that larger controlled trials of Ketamine may be helpful in determining exactly which patients should be treated and how exactly the Ketamine should be administered for best effect. [Dr A] has a very long history of involvement in drug development and clinical trials and would be well positioned to conduct such trials. He would also be aware that simply using Ketamine clinically in the way in which he did, may build up some impression of its usefulness used in this way but that this did not constitute a clinical research trial ... However, there was clearly no systematic characterisation of patients in the way in which would be expected if the patients were going to be reported as an open label trial⁸ and the patients were extremely heterogeneous.”

67. The consultant psychiatrist/researcher considers that the activity in which Dr A was engaged is best classified as clinical audit. He noted that clinicians in New Zealand are encouraged by their professional bodies to conduct clinical audits and that, for many years, clinicians have been encouraged to publish such audits. With regard to whether retrospective or expedited ethical review would have been preferable before reporting data from the patients who received ketamine treatment, the consultant psychiatrist/researcher commented that this is an ethical debate about which there are many opinions.

Experimental treatment?

68. Dr A said that he does not consider that there is a black and white answer as to when the point has been reached with regard to safety and efficacy of a treatment to be able

⁸An open-label trial or open trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered. This contrasts with single blind and double blind experimental designs, where participants are not aware of what treatment they are receiving (researchers are also unaware in a double blind trial).

to say that the evidence is sufficient for clinical use. For example, there is no required number of randomised controlled trials (RCTs).

69. Dr A said that the safety of ketamine was well established, as it had been used for 50 years for analgesia.
70. Dr A stated that, at the time he treated Patient 1, there were two placebo controlled studies and 100–150 case reports regarding the use of ketamine for TRD, which he considered amounted to a very strong literature base. He said that because the crossover design used in these studies⁹ is an incredibly powerful design, both in clinical and statistical terms, relatively few people are required for the studies to be robust.
71. The Zarate study showed that 35% of subjects maintained a response to ketamine for at least a week. With regard to those patients who responded for only a short period of time before becoming depressed again, Dr A considered that it was beneficial for those patients to have had relief from what was a “truly horrifying experience”, and said that a small number of individuals recovered fully. In his view, the only issue was that there are some aspects of best possible dose that have not yet been defined, such as whether the dose being used is the best dose and whether it is being used in the best possible way. However, he noted that even though there is more to learn, it does not necessarily mean that what has been done in the past was inappropriate.
72. Dr A advised that although the published studies involved the intravenous administration of ketamine, the drug is administered intramuscularly for pain relief, and the product information sheet states “for IM and IV use”.
73. Dr A stated that when ketamine was originally used there was no reason why intravenous administration was chosen, and he considered that intramuscular use was appropriate. He said that intravenous use is inconvenient as it requires setting up an infusion pump, a lot more checking on patients, and then an hour “to break it down” after treating the patient. An IM injection is more convenient as it takes only 30–40 seconds. Dr A advised HDC that the IM injection was chosen for clinical convenience and he was not intending to compare the effectiveness of IM injection against IV use.
74. Dr A said that the pharmacokinetic profile that was set up for IM injections means an earlier peak with some earlier drop-off in concentrations. In the case of an IV infusion, as soon as the infusion is stopped there is a drop in concentration. He said that, in his view, an IM injection would give the same exposure to ketamine as an IV infusion.

⁹A crossover study is a longitudinal study in which subjects receive a sequence of different treatments (or exposures). While crossover studies can be observational studies, many important crossover studies are controlled experiments. In a randomised clinical trial, the subjects are randomly assigned to different arms of the study which receive different treatments. A crossover clinical trial is a repeated measures design in which each patient is randomly assigned to a sequence of treatments, including at least two treatments (of which one “treatment” may be a standard treatment or a placebo). Nearly all crossover designs have “balance”, which means that all subjects should receive the same number of treatments and that all subjects participate for the same number of periods. In most crossover trials, each subject receives all treatments.

Dr E

75. Dr E is employed as a consultant psychiatrist with the DHB.
76. Dr E advised that he recalls prescribing ketamine for two patients on Ward X (Patients 2 and Patient 8 — see **Appendix C**) as part of their treatment for TRD. He stated that he recalls much discussion among the psychiatrists in the region about its use at that time.
77. Dr E stated: “My colleague on [Ward X], [Dr A], showed me a positive randomised controlled trial. This, along with its safety record, made me comfortable prescribing it. As it was an unusual intervention, quite detailed written information was supplied to patients and written consent obtained. Patients were monitored quite closely throughout the procedure.”
78. Dr E was asked whether he could recall when the consultant peer review group first discussed the prescribing of ketamine for TRD. Dr E could not recall the exact date but considered that the discussions occurred at the time that he, Dr A and psychiatrist Dr H were working on Ward X together, which was from late 2009. Dr E recalls that in addition to himself, Dr A, Dr H, Dr Q, and later Dr P, attended the meetings.
79. Dr E believes that the discussion preceded the initial prescribing of ketamine in April 2010. He stated that the discussions were informal but included references to the evidence base and literature. He cannot recall any concerns about ketamine treatment being raised in that forum.
80. Dr E said that later he was “involved in administering ketamine to a patient of [Dr A]”, and that the reason for his involvement was that “the District Health Board had advised [Dr A] to involve a colleague”.
81. Dr E stated: “The use of ketamine was purely driven by clinical circumstances. No trial was being conducted.”

Dr H

82. Dr H advised that he is a member of the local consultant psychiatrist peer review group. He recalls that in 2010 the other members were Dr A, Dr Q, Dr P, and Dr E. He thought that there might be records of attendance, but no minutes were taken.
83. Dr H recalls discussions about ketamine treatment in the group meetings prior to April 2010. There was discussion about the literature and evidence base. He recalls that Dr A mentioned that it was a useful treatment, that ketamine had a long history of use for pain and analgesia, and that the data for use in treating depression included RCTs.
84. Dr H stated that he thought the two RCTs provided very good data and there was an adequate evidence base. He recalls that Dr A indicated that he had obtained some feedback on the use of ketamine for TRD via the university.¹⁰

¹⁰ See below regarding the feedback the Health Research Council sent to the University.

Dr D

85. Dr D is a psychiatrist with management responsibilities at Southern DHB.
86. Dr D advised that prior to late November/early December 2010 he was not aware that ketamine had ever been used as a treatment for depression. He stated that he has never prescribed ketamine.
87. Dr D said that on 29 November 2010 the consumer advisor, Mr C, brought to Dr D's attention Dr A's off-label prescribing of ketamine. Prior to this, Dr D was unaware that off-label prescribing of ketamine had been occurring.
88. Dr D stated that it would not be usual for him to routinely seek information regarding the prescribing habits of vocationally registered psychiatrists employed by the DHB. He stated: "I understand that [Dr A] had involved his employer ([the university]) earlier when seeking advice regarding enquiries made into his prescribing of ketamine. He must have made the assumption that I did not need to be informed at that stage."
89. Dr D advised that from 29 October 2010 he engaged in email and verbal communications with Mr C and Dr A about the issue, but he did not record any notes during the verbal discussions. Consequently, the email exchanges are only a partial account of the discussions that took place.
90. Dr D stated:

"On reviewing my initial emails exchanged with [Mr C] and [Dr A] (early December 2010) it is apparent to me that I was still working out the correct terminology to use when describing the off label prescribing of ketamine. In one of the emails I used the term 'experimental' but on further discussion with [Dr A] it seemed to me that the word 'experimental' should be used only to refer to treatments for which there is a negligible evidence base. Early in my discussions with [Dr A] I was reassured by him that although the evidence base for the use of ketamine in treatment resistant depression was not extensive, it was however, adequate to support off label prescribing in everyday clinical practice."
91. Dr D noted that, given Dr A's years of experience in the field of psychopharmacology, he deferred to Dr A's judgement regarding the clinical usefulness of ketamine as a treatment for depression.
92. Dr D stated that it is his belief that Dr A's prescribing of ketamine for TRD is an example of prescribing an approved medicine for an unapproved indication where the evidence base for the safety and efficacy of such prescribing is present but not extensive and where the use of the medicine for the indication in question is not a common practice.
93. Dr D stated that by late 2010 he had formed the opinion that Dr A's off-label prescribing of ketamine should be viewed as a case of "novel" off-label prescribing rather than being viewed as "experimental" treatment. Dr D stated: "I did not think Dr A's prescribing had significantly departed from standard practice *without justification*

nor did I believe there was reasonable evidence that his prescribing had compromised patient safety.” At that stage, it was Dr D’s opinion that, given the level of interest in Dr A’s prescribing of ketamine, it would be wise to ensure that all of the patients who wanted to be treated with ketamine signed a consent form to that effect. Dr D stated that Dr A accepted the rationale for requiring written consent and agreed to obtain it.

94. Dr D stated that during December 2010 and early 2011 he discussed Dr A’s off-label prescribing of ketamine with a number of people at the DHB and the university. Dr D stated that he also raised the issue at a meeting of psychiatrists. He said that during these meetings he sought reassurance that his categorisation of this prescribing as “novel” off-label prescribing (rather than “experimental” prescribing) was accurate. He stated: “As a result of these discussions, I felt reassured that I was on the right track.”
95. In December 2010, Dr D asked a senior medical manager at the DHB whether he thought it was appropriate to carry out an external review of Dr A’s prescribing. The senior medical manager responded that he did not think an external review would be required at that time.
96. Dr D advised that the DHB has a “medicines review group”. Dr A is a member of the group. The group has prepared a policy (finalised on 19 January 2012) for the use of unapproved medicines in the DHB. According to the policy, when prescribing an approved medicine for an unapproved indication, in the absence of evidence from “well conducted clinical trials”, the SMO must:
 - consult with at least one other SMO colleague and document the outcome in the patient record; and
 - obtain written patient consent.
97. Dr D stated that when HDC advised the DHB of its intention to investigate this matter, a senior medical manager banned any off-label prescribing of ketamine for psychiatric disorders. Subsequently, two patients who were receiving regular IM injections of ketamine approached the DHB and requested that they be allowed to continue treatment. Both reported that the treatment had been of significant benefit to them. With the senior medical manager’s approval, Dr D arranged for both patients to continue receiving ketamine injections. Dr D met with the patients and explained the controversy surrounding Dr A’s off-label prescribing of ketamine, and the patients signed a consent form verifying that they understood the nature of the treatment set in the context of the controversy that had arisen.

Dr F

98. Consultant psychiatrist Dr F provided information regarding the circumstances in which Patient 5 was offered ketamine treatment.
99. Dr F advised that Patient 5 had experienced increasingly low mood, which had failed to mitigate with Dr F’s usual therapeutic inputs, including extra session times and medications. He stated that Patient 5 had been seriously unwell in March 2011.

100. Dr F advised that a few days later he had a discussion with Patient 5 about the possibility of her starting ketamine treatment. He stated:
- “This seemed to me to be a medication that might be useful to her from the point of view of her mood and also offer her a psychodynamic way out of her difficulties where she seemed completely stuck. I also confirmed with [Dr A] that she might be a possible candidate for this treatment and we discussed that this would have to be on a voluntary basis.”
101. Dr F advised that Patient 5 had read papers and information about ketamine prior to starting the treatment. He noted that she had a medical background. He said he had seen some papers about it and that he explained to Patient 5 how he thought it worked.
102. Dr F advised that Patient 5 was “under the Mental Health Act on 1 April and discharged from the Act on 6 April 2011”. He said that Patient 5 signed the consent for her initial treatment with ketamine on 7 April. He said he warned Patient 5 that there was no guarantee that ketamine would work but, in the circumstances, he thought it was worthwhile attempting it.
103. Dr F said he had heard a presentation from Dr A about ketamine and also heard a lecture on the literature relating to ketamine from American trials. Dr F said that he had also read journal articles about ketamine trials at sub-anaesthetic doses for low mood.
104. Dr F stated: “[I]n my view overall I think [Patient 5] has done particularly well having been free of self-harm or overdoses or admissions to hospital for over a year compared to [many] self-harming attempts the year prior to starting it.”

Dr I

105. Psychiatry Registrar Dr I advised that between December 2010 and December 2011 she had two consecutive rotations of six months each on Ward X under the supervision of Dr A.
106. Dr I stated that during that period she witnessed Dr A’s involvement with several patients who were admitted for the day to have ketamine injections. She stated that on at least two occasions she observed Dr A go over the consent process.
107. Dr I stated: “I am confident that the consent process was thorough and unbiased — topics such as ‘off label’ medications, RNZCP Guidelines, pros and cons, alternative treatments and ‘you can change your mind at any time’ were mentioned.” Dr I advised that she was unable to recall the patients’ names.

RN M

108. Registered Comprehensive Nurse RN M said that nursing staff had very little direct input into the ketamine programme. He stated that there were protocols regarding the initiation and maintenance of the programme, which were to be carried out by medical staff.

109. RN M advised that he remembers the conversation Dr A had with Patient 9 about ketamine. RN M stated that Patient 9 had a previous awareness of the drug and seemed surprised that it was a treatment to be considered. She called the drug “horse tranquiliser” and knew it was sometimes a drug of abuse.
110. RN M said that Dr A explained to Patient 9 that the rationale for the use of the drug was that it would help guide further decision-making regarding what would be the most effective long-term pharmacological treatment for her. RN M stated:

“I believe [Patient 9] was able and competent to give consent, was well informed and, in my view, had a good understanding of the rationale for the treatment. I did not document consent processes as I believed that as the use of the drug in this manner was an ‘off label’ use (this was verbally explained to [Patient 9]) and the whole programme came under the auspices of direct medical supervision ... As it transpired the treatment was not particularly successful and was stopped in favour of psychological interventions.”

RN N

111. RN N advised that on the occasions he attended the administration and post-administration observation of patients receiving ketamine he “clearly heard [Dr A] outline the procedure to the recipient and obtain consent to proceed with the treatment. This was certainly the case for the patient identified as ‘[Patient 6]’”.
112. RN N advised that Dr A had specific expectations of nursing staff attending the patient following the administration of ketamine. Their role was to complete the physical observations of the patient and observe and report any side effects seen, as he did for Patient 6.

Information from patients

113. A number of the patients who received ketamine treatment were contacted by HDC (see **Appendix C**) and their comments are as follows.

Patient 5

114. Patient 5 advised that she found the information given to her prior to treatment to be “really good and really helpful”. She stated that she found the written information sheets to be helpful as she has a science background and liked the references to the study/literature.
115. Patient 5 said that she thinks she also had verbal discussions about ketamine. She recalls discussing the treatment with her psychiatrist and her parents and did not feel she had any outstanding questions about it at the time.
116. Patient 5 said that the treatment worked for about two and a half weeks to three weeks after the injection, and she has remained on ketamine. She said that it was a “lifesaver” treatment and she receives an injection every three weeks.

Patient 7

117. Patient 7 stated that she was unable to recall a lot of details around receiving ketamine treatment at the public hospital in 2010. She cannot recall receiving any written information or signing anything, but can recall that she primarily asked about possible side effects. She stated that she spoke directly with Dr A, and she was very comfortable with what was discussed with her regarding the treatment, and had no concerns at the time about the treatment.
118. Patient 7 stated that she had two injections in 2010 and had no side effects. She stated that she found it beneficial for three to four days to get her through the issues she was experiencing at the time.
119. Patient 7 stated that she had some post-treatment discussions with Dr A but these mainly centred on her other medications and changes to her medications.
120. Patient 7 gave HDC her consent to approach her mother, as her notes indicated that her mother had raised some concerns at the time. HDC contacted Patient 7's mother, who advised that her concerns had been that Patient 7 might not be able to make a sound decision about her treatment because of her condition and her deep depression. She advised that Patient 7 usually made her own decisions. She was aware that her daughter was receiving medication but was not given any details of her daughter's treatment by staff.

Patient 4

121. Patient 4 advised that he had no concerns about the information or consent process. He said that he had a long history of headaches, which had responded to anaesthetics at times. He had some long-term depression but it was not clear whether his headaches were caused by depression or vice versa.
122. Patient 4 advised that his admission to Ward X was discussed with Dr P, as was ketamine use. Patient 4 was admitted for three to four days.
123. Patient 4 stated that he was happy about the consent process and the level of information given to him (some written) by Dr A. Patient 4 said that he gave both verbal and written consent, and he knew what was going on, as did his wife.
124. Patient 4 could not recall the term "off label" being discussed, but it was a long time ago. He recalled that he was told by Dr A that about half of the people who used ketamine were helped by it. Patient 4 said that he did not get much relief from using it.

Patient 6

125. Patient 6 could not recall anything about the issue and was unable to assist.

Patient 2

126. Patient 2 advised that she was a voluntary patient and received ketamine for only a short period. Patient 2 stated that the ketamine worked but "the effects didn't last".

127. Patient 2 cannot recall having any concerns about the information provided or the consent process.

Patient 3

128. Patient 3 stated to HDC that he had no concerns about the information or consent processes regarding ketamine use.

Patient 1

129. Patient 1 said that she had heard from other people about the ketamine issue. She confirmed that she received ketamine treatment, but cannot recall anything about the events around that time. She has since had outpatient treatment with ECT and said that her memory and recall are not very good.

Other patients

130. Of the remaining patients, one is deceased, one was unwell and unavailable to speak to HDC staff, and one did not respond to phone messages or letters. One other patient wrote a letter to the National Health Board supporting the use of ketamine, but did not wish to be interviewed.

Anonymous patient

131. The partner of a patient who was admitted to Ward X with depression stated that the patient was seen by Dr A, who asked the patient if he would like to be in a drug trial for ketamine. The partner stated that she was present during the conversation. The partner was aware that ketamine is a tranquilliser used by vets and was not happy for the patient to be in the trial and said her partner declined to take part in it.
132. Dr A does not recall discussing ketamine with this patient, and no reference to this conversation is recorded in the patient's records.

Mr S

133. Mr B advised HDC that Mr S was a patient in Ward X in October 2011 and had been approached about the use of ketamine for depression. HDC contacted Mr S, who advised that he could not recall the exact dates of admission as he had been on and off a compulsory treatment order.
134. Mr S said that he thinks he was approached about ketamine use about two years ago by Dr E, not Dr A, but he could not recall the exact details. He said he was aware that it was not a conventional treatment, and he thinks he was given some written information, but is unsure. He said that his family members were not involved in his decision, and he was "not forced at all". Mr S said that he declined treatment with ketamine.
135. Dr E advised that Mr S asked for and was given information about the possible use of ketamine. Dr E considers that such treatment came to Mr S's notice because other patients on the ward had received ketamine, and it may also have been discussed in the regular "medicine group" run by the pharmacists for the patients.
136. Dr E said that he did not recommend ketamine for Mr S.

Research funding

HRC

137. The Health Research Council (HRC) confirmed to HDC that Dr A submitted an expression of interest in October 2009 relating to a research project.¹¹ On 16 December 2009, the HRC sent feedback correspondence in an email to the Research Office of the university, notifying the university of the outcome of HRC's assessment of the proposals submitted to the HRC from that institution.
138. The email is pro forma, with a spreadsheet attachment listing results for that institution for the funding round. Dr A's project was not selected to proceed to full application. There is no specific feedback tailored to the individual application. The HRC confirmed that correspondence from the HRC is directed to the host institution, rather than individual investigators, as research proposals are submitted by the institution rather than investigators. There was no subsequent correspondence from the HRC to the university or to Dr A.

Funding grant

139. Dr A told NHB and HDC staff that in November 2009 he applied to a grant funding organisation for research funding to examine the ketamine dose finding/dose-response relationship in a more rigorous way.
140. The application was declined. Dr A said that he received feedback from the funding organisation advising that the proposal was not novel and that it had no value or utility. Dr A told the NHB that the feedback was blind. However, Dr A could not locate a copy of the feedback provided to him in this case.
141. Dr A recalls a reviewer sending him some tailored individualised feedback and stated that "some of the feedback I got from the reviewer was this is scarcely a novel finding". He could not recall precisely, but believed the reviewer was Mr R. Mr R's feedback to Dr A included the following comment: "... given previous favourable results, would there be any utility in offering low-dose non-responders an open trial of 0.5mg/kg?".
142. Funding organisation staff advised that they met in November 2009 and wrote to Dr A at the university in December 2009 declining the application on a funding availability basis. The application received a grade of B (a project that has priority for funding and is funded if the Committee has sufficient funds available after funding B+ applications).
143. Mr R informed HDC that, in August 2009, Dr A asked him to review his proposal to the funding organisation. Mr R agreed to do so, and was sent the proposal on 5 August 2009.
144. Mr R said that reviews are normally sent to the requesting agency (such as a journal or granting body). Mr R does not recall being contacted directly by funding

¹¹ The expression of interest referred to treatment with ketamine.

organisation staff and so he felt it would be appropriate and useful to send his one-page review directly to Dr A, which he did on 23 November 2009.

Reporting by Dr A

Scientific meeting 2010

145. When asked when he first decided to share information about patient responses to ketamine for treatment-resistant depression, Dr A said that he presented his observations overseas at a scientific meeting for psychiatrists in late 2010.¹²
146. Dr A advised the NHB that he was contacted by the organisers shortly before the meeting, because the local college, the New Zealand College of Psychiatrists, did not have a representative on the panel organising the conference, and so he agreed to be the representative.
147. Dr A said that well after the meeting submission date had closed, the convenor of the conference requested that he put together an abstract. He said that he took his “standard ketamine talk” and added information about his general sense of how the patients on Ward X had responded, and made reference to the response information for patients Patient 1 and Patient 7, who had consented to his use of their information.
148. Abstracts for the conference were published.
149. The conference organiser confirmed to HDC that Dr A’s abstract for the late 2010 conference was accepted after the advertised closing date. The conference organiser advised HDC that it is not unusual for some abstracts to be accepted after the deadline. However, he could no longer locate Dr A’s 2010 abstract submission in the database to confirm the exact date it was received.
150. Dr A told HDC that the slides he prepared for the presentation were prepared on 12 October 2010. Both the abstract and presentation slides refer to Dr A’s local experience of 10 adult patients receiving ketamine. The medical and drug administration records supplied to HDC by the DHB show that by 1 September 2010, five Ward X patients had received ketamine, and by 1 October 2010, seven Ward X patients had received ketamine.
151. Dr A said that the abstract was written at the last minute and he described 10 patients as an “estimate”, which was an error. Dr A said during his interview with NHB staff that six patients had received ketamine by September 2010. Dr A acknowledged to NHB that the final sentence of the abstract, “[t]rials with amantadine and procyclidine ... are underway” was also incorrect. He said that his intention was to do a trial with amantadine and procyclidine, but this did not eventuate.
152. Dr A told HDC that the number of patients featured in the abstract was incorrect, and that he thought only five patients had been treated with ketamine at the time he submitted his abstract. Dr A’s explanation to HDC was that he had seen five individuals, some of whom had had multiple treatments, and that this was a best

¹² Also presented in NZ in October 2010.

estimate written late at night to be submitted that night, and that he had made a mistake. He said that “[t]he other information in [the abstract] apart from that ten which should be five is correct”.

Responses to the provisional opinion

Dr A

153. In addition to those included elsewhere in this report, Dr A submitted as follows in response to the provisional opinion:

- It is “sad to observe” that treatment with ketamine of patients suffering from TRD was withdrawn during the investigation, and over that period “patients’ opportunities for treatment with Ketamine increased internationally”.
- In joint clinical appointments, research informs practice and practice informs research, and it is not possible to separate the two.
- Peer group meetings are almost invariably “protected quality assurance activities and by their very nature records of discussions are not made”. Issues such as off-label prescribing are frequently discussed at peer group meetings in a free, frank and confidential manner. To be required to keep a record of such discussions would “totally change the nature of such peer group discussions” and such a recommendation “may well be contrary to the quality assurance provisions of the HPCA Act”.
- The adverse comment about him is unduly harsh because it relates principally to lapses in record-keeping and documentation.
- The investigation has been stressful and distracting, and he has cooperated fully with the investigation.

Southern District Health Board

154. Southern DHB responded that the report is “a most useful guide” for its “re-development of policies surrounding off label prescribing, the DHB/university interface on employment responsibilities, and the need for clarity amongst the workforce of these policies”.

155. The DHB stated that it will undertake individual, but linked work streams to progress HDC’s recommendations within the allocated time frame.

Standards

156. The New Zealand Medical Association Code of Ethics provides:

“49. Boundaries between formalised clinical research and various types of innovation have become blurred to an increasing extent. Doctors retain the right to recommend, and any patient has the right to receive, any new drug or treatment which, in the doctor’s considered judgement, offers hope of saving life, re-establishing health or alleviating suffering. Doctors are advised to

document carefully the basis for any such decisions and also record the patient's perception and basis for a decision. In all such cases the doctors must fully inform the patient about the drug or treatment, including the fact that such treatment is new or unorthodox, if that is so.

50. In situations where a doctor is undertaking an innovative or unusual treatment on his or her own initiative, he or she should consult suitably qualified colleagues before discussing it with, or offering it to, patients. Doctors should carefully consider whether such treatments should be subject to formal research protocols.”

157. The Royal Australian and New Zealand College of Psychiatrists Practice Guideline #4, *“The use of Medication in Dosages and indications outside normal clinical practice”*, provides as follows:

- “1. Prescription of medication in doses above usually accepted ranges or outside usual indications is recommended to be reserved for those patients where standard treatments have failed or is considered inappropriate. The reasons that require the non standard treatment should be clearly and accurately documented, along with a thorough assessment of the patient's diagnosis and clinical (both mental and physical) state.
2. Consultation with an experienced colleague is recommended, including consideration of a formal written request for a second opinion on treatment options, prior to commencing treatment. Documentation of the evidence that substantiates the new treatment plan will help to support the decision.
3. Relevant monitoring, including therapeutic serum level monitoring where available, should be undertaken and recorded. Appropriate vital signs and other physical signs should be monitored regularly as needed. Clinical progress should be monitored at a frequency appropriate to the patient's mental and physical status.
4. Some treatments may be so significantly beyond normal clinical practice and lacking in an evidence base that they could be considered to constitute an experimental treatment. Such treatment should be referred to an appropriate Institutional Ethics Committee for advice and review.
5. Informed consent should be obtained and recorded. If the patient is deemed not competent to give informed consent, such treatment should only be given if the patient is being treated under the appropriate local legal framework and with the support of an independent second opinion (Note: in New Zealand such a second opinion should be by a psychiatrist approved by the Review Tribunal for the giving of such opinions). The patient may withdraw consent at any time.
6. An end point should be decided as part of the overall treatment plan to determine whether the treatment should continue or be ceased. The parameters for this should also be discussed with the patient, where possible, and documented. Before initiating such treatment the management plan should contain a maximum duration of treatment to be undertaken to assess

benefit. Continuation of the treatment may proceed with documentation of the benefit and with specific ongoing review of progress.”

Opinion: Dr A — Adverse comment

Introduction

158. The Code is about consumers and their rights, and the issue of informed consent goes to the heart of the Code. My Office talked with many of the consumers at the centre of this inquiry. No consumer, either before or after the inquiry commenced, has complained to HDC. No consumer interviewed felt they received insufficient information. HDC has not been told that any consumer believed they were harmed. It is notable that two consumers, who benefited from this treatment by the alleviation of their severe psychological pain, asked specifically for the treatment to be continued when there was a risk that it would be stopped.
159. The factual background in this matter is not disputed. From April 2010, Dr A treated with ketamine 11 patients who were suffering from TRD (see **Appendix C**).
160. Between 19 April 2010 and 13 September 2010, six patients were treated with intramuscular injections of ketamine. These six patients were not asked to sign a consent form, but the clinical notes document that there was a discussion with each patient about the use of ketamine, and the patients gave verbal consent to the injections. The DHB confirmed that all patients were given written information about the use of ketamine for treating TRD.
161. On 20 September 2010 an information/consent sheet was created. All of the five additional patients subsequently treated with intramuscular injections of ketamine for TRD signed this information/consent sheet, which included statements that they had “read [the] information sheet” and that they had “had a chance to discuss any questions” and that they agreed “to have a ketamine injection for [their] depression”.
162. Following concerns expressed by HDC that the information/consent sheet did not inform patients that use of ketamine for depression was “off-label” use, the form was modified in April 2011 by the inclusion of a sentence to the effect that the use of ketamine in this way is what is termed “off label”.
163. No patient has complained to HDC either about the informed consent process or about the provision of ketamine.
164. The Code provides in Right 7(6) that:

“[w]here informed consent to a health care procedure is required, it must be in writing if—

 - (a) the consumer is to participate in any research; or
 - (b) the procedure is experimental”.

165. It is therefore important, in terms of the informed consent process, whether or not the prescription of ketamine in these circumstances amounted to research or constituted an experimental procedure.

Issues

166. The key issues to be decided in this matter are as follows:
- Was the prescription of ketamine research?
 - If it was not research, could the prescription of ketamine be categorised as an experimental procedure?
 - Were the relevant practice guidelines complied with when prescribing ketamine off label?

Summary of the expert advice

167. I obtained expert advice from two independent psychiatrists in relation to this investigation. The views of the two experts are similar in some respects but diverge on some key issues. A general summary of their advice (set out in full in Appendix A and Appendix B) follows.

Dr Allen Fraser

168. Adult General Psychiatrist Dr Allen Fraser took the view that the prescription of ketamine described above was not research, but was uncommon off-label prescribing. He advised that “on the basis that treatment-resistant depression, by definition, is not responsive to standard treatments, I believe that the published literature is positive enough to justify off label prescribing of ketamine for patients with a treatment resistant Major Depressive Episode”.
169. As ketamine has not been approved for treating depression in any jurisdiction, Dr Fraser categorised the prescription of ketamine in these circumstances as off-label use for an indication where use for that indication was not common.
170. In relation to Dr A’s recording of the results of ketamine use, Dr Fraser advised:

“The patients were not invited to participate in a research study, because this was not research in that sense. As I would expect of any clinician prescribing off label in this way, [Dr A] monitored the effects of the treatment, and collected data to allow evaluation of what were the effects of the treatment. This should be seen as a form of clinical audit rather than clinical research. Failure to have done so would attract strenuous criticism, as he would not have had objective data to evaluate the treatment.”

Associate Professor Wayne Miles

171. Psychiatrist Associate Professor Wayne Miles advised that, across the clinical spectrum, one would find a range of definitions and positions on the meaning of research. He believes that there would be a general view that clinical research spreads across intervention study, observation study and innovative practice. Associate Professor Miles said he considers the evidence justifies further controlled study to

properly test the efficacy and safety of ketamine for treatment of TRD, but he would not himself be persuaded that the current evidence is sufficient to use it as a treatment now.

172. Associate Professor Miles noted, however, that there is a “legitimate middle ground” between research and off-label clinical use, which allows “innovative treatment”.
173. Associate Professor Miles considers that the use of ketamine in this situation was an innovative treatment. He noted that this was partly because the ketamine had been used intramuscularly while the existing evidence related to intravenous use. As such, he noted that the following processes should have been put in place:
- Properly conducted and well recorded discussion with peers and other relevant experts in the field.
 - Depending on the collective advice, submission of the innovative treatment to an Ethics Committee.
 - Design of an appropriate use and monitoring protocol.
 - Design of an appropriate information sheet and consent form.
174. Associate Professor Miles noted that, although it was not evident to him whether peer review had occurred before the decision to embark on the use of ketamine, it is clear that over the time period in question a number of local psychiatrists were aware of the prescribing and some were quite closely involved in treatment reviews and decisions.
175. Associate Professor Miles is of the view that “the main point of departure from what [he] considers to be appropriate standard of care was in the consideration of the type of treatment, its novelty, and the need to apply regulations pertaining to the innovative treatment”. He stated that this departure is a moderately severe departure from the New Zealand Standards and Guidelines. However, Associate Professor Miles recognised that the involvement of other [local] psychiatrists suggests that his peers do not share his interpretation of the innovative nature of this treatment. Similarly, he noted, the DHB management do not appear to have seen the use of ketamine in this situation as innovative treatment requiring different consideration than would have been applied to off-label use with a high evidence base.

Was the prescription of ketamine research?

What is research?

176. Twenty-five years ago, Judge Silvia Cartwright (as she then was) explored the meaning of research in the report of the Cervical Cancer Inquiry.¹³ Judge Cartwright defined medical research as “a systemic and organised activity which clearly goes beyond normal service or treatment requirements and which has the potential to advance knowledge in a field relevant to human health”.¹⁴

¹³ *The report of the Committee of Inquiry into allegations concerning the treatment of cervical cancer at National Women’s Hospital and other related matters*, Auckland, Committee of Inquiry, 1988 at 132–134.

¹⁴ *Ibid* page 61.

177. Judge Cartwright stated that there are three requirements to establish the point at which good clinical practice involving systematic observation warrants a research label.¹⁵ They are:
- A clear intent on the part of the investigator that involves more than the observation or management of individual patients.
 - A statement or the inference of a hypothesis (something that the investigator is attempting to prove or disprove).
 - Evidence of advanced planning for managing a clearly identifiable group of patients by a method that differs from the way in which other patients with the same disease are managed.
178. Historian and philosopher Dr Tim Lewens has stated in an article in the *Journal of Medical Ethics* that discussions on what distinguishes research from treatment are “thin on the ground”.¹⁶ He argued that research and treatment should be distinguished on the basis of their functions, and for an activity to be classified as research it is, at least, necessary that its function is the generation of knowledge. The author must have planned or structured the activity to bring about the attainment of knowledge. He stated: “Treatment aims at improving health. Research aims at generating knowledge. Sometimes treatment, understood in this way, will contain episodes that can be termed research: a series of diagnostic procedures will yield a piece of new knowledge, for no one would have known what was wrong with the patient before.”
179. However, Lewens argues that the generation of new knowledge, when a doctor’s efforts to acquire that knowledge are subordinate to a more general plan to set about improving the patient’s health, will not trigger the kind of ethical concern that the distinction between research and treatment seeks to capture.
180. Philosopher Professor Raanan Gillon opined in an article in the *Journal of Medical Ethics*¹⁷ that the difference between treatment and research is that, in the case of treatment, the issue of a patient being used to benefit others does not arise, and the focus of the doctor is on the overall benefit of the patient.
181. Professor Gillon considers that there is a therapeutic/non-therapeutic spectrum, and the assessment of therapies is not unequivocally at either end of the spectrum. He said: “To the extent that there is prior reason (though not yet scientifically validated reason) to believe that the intervention under investigation will benefit the patient more than current best available treatments — or harm the patient less — the intervention is at the ordinary medical treatment or therapeutic end of the moral spectrum.” He proposes that the test to use is whether the doctor would normally have good reason to subject the patient to the particular intervention in order to try to optimise the patient’s medical management and treatment. If so, in his opinion, the norms of medical treatment apply.

¹⁵ Ibid page 63.

¹⁶ Lewens, T, “Distinguishing treatment from research: a functional approach” (2006) *J Med. Ethics* 32:424–429.

¹⁷ Gillon, R, “Medical treatment, medical research and informed consent” (1989) *J Med Ethics* 15:3–5.

Was the prescription of ketamine research?

182. The first question in determining whether the provision of ketamine to these 11 patients amounted to research is whether Dr A's primary intention was to provide treatment to these patients, or whether it was to generate knowledge.
183. Both Dr A and Dr E have stated that the primary purpose was the treatment of patients with TRD. When asked whether he was testing a hypothesis in treating patients with TRD with ketamine, Dr A responded: "I guess if you want to look at it in hypothesis terms, it's 'can we make them better?'" Dr E commented that "[t]he use of ketamine was purely driven by clinical circumstances. No trial was being conducted."
184. Although Dr A administered ketamine via IM injections rather than the IV route as used in the research studies, he explained that this was for convenience and ease of administration and, in his view, did not significantly alter the treatment from the reported studies. He noted that ketamine has been approved for both IV and IM administration (as is stated in the Ketalar Data Sheet) and he was clear that he was not intending to compare the effectiveness of the two routes. I accept that no comparison between routes of administration was intended.
185. Dr A advised HDC that ketamine was used for "unselected individual" patients in a ward setting. The patients who were offered treatment with ketamine were those who presented in Ward X with TRD at the relevant time and met the clinical criteria set out above. Dr A advised that, accordingly, there was no obvious control group to allow comparison with patients receiving other treatments.
186. I accept that the patients were a diverse group (other than all having been diagnosed with TRD) and that Dr A did not view the prescription of ketamine as research or intend the treatment to answer a broader research question.
187. Dr A, Dr F and Dr E all accepted that the evidence available to them was sufficient to justify the use of ketamine for their patients. In addition, Dr H and Dr D both told HDC that they considered there was an adequate evidence base to support prescribing ketamine to patients as part of clinical practice, rather than as research.
188. I accept that Dr A held this view of the available evidence and was supported in this view by his colleagues. I also note the advice of my expert advisor, Dr Fraser, that the prescription of ketamine in these circumstances did not amount to clinical research.
189. I find that it is more likely than not that the prescription of ketamine was primarily for the treatment of patients with TRD, rather than constituting clinical research.

Presentation

190. However, it remains of concern that in October 2010, when he had treated only seven patients with ketamine, Dr A submitted an abstract stating that "mood response data in 10 adult patients with treatment resistant major depression has shown substantial (> 50% reduction in MADRS scores) by 24 hours in half, with excellent safety and tolerability". Subsequently, this mistake was repeated in the presentation at the meeting. In response to the provisional opinion, Dr A explained that this occurred because of "the very pressured circumstances which led to that presentation".

191. I have no evidence that Dr A attempted to recruit more patients to achieve this number (I note that Dr A advised that there were no patients commenced on ketamine between September 2010 and January 2011 because none presented in Ward X who were appropriate for the treatment). While I accept that patients were not recruited for research purposes, I consider that Dr A should reflect on the need to exercise caution in situations where his clinical and research activities may overlap, and to ensure that his reporting of his work properly and accurately describes what has been done and in which context. I remain of the view that, in a situation such as this, there is a risk that treatment will be viewed as having been incorporated into, and having formed part of, the research output of the clinician/researcher, and that such suspicion may be accentuated if a clinician/researcher's reporting of his or her activities is inaccurate.

Was the prescription of ketamine experimental treatment?

192. Having concluded that the prescription of ketamine was treatment rather than clinical research, the next issue is whether it constituted an "experimental procedure", in terms of Right 7(6)(b) of the Code. As noted above, experimental procedures require written consent under the Code.
193. According to one of my experts, Dr Fraser, experimental prescribing "suggests that there is no clear opinion held by the clinician as to what is the likely outcome". He distinguished this from off-label prescribing where, "although the medication may not be registered for the particular indication, there is evidence to support the prescription", noting that the off-label prescribing may be rare or common among one's colleagues. Dr Fraser concluded that there was sufficient evidence to justify off-label prescribing for ketamine in patients with TRD. He described it as an uncommon treatment approach for a disorder in which common approaches are frequently unsuccessful.
194. Associate Professor Miles advised that he believes there would be a range of positions in relation to the point at which the evidence base regarding the safety and efficacy of a treatment is such that it would be considered sufficient to support off-label prescribing of the particular medication for a specific clinical indication. He stated: "I suspect the majority would want evidence that the treatment has been used in humans safely and also have a modest degree of reported evidence that it does have a desired effect in the condition under question."
195. Associate Professor Miles advised that a conservative position would require Randomised Control Trial (RCT)¹⁸ evidence, but many clinicians would be prepared to contemplate less. In his view, safety data in humans is essential, and there would need to be either case reports attesting to benefit or a strong theoretical/physiological argument for the product having the potential to produce benefit.
196. Associate Professor Miles noted that he would not himself "be persuaded that the current evidence would be sufficient" to use ketamine to treat TRD at this point in time. He then went on to state that if contemplating the use of ketamine in an "innovative treatment sense", consultation with peers would be required, likely

¹⁸ See footnotes 5 and 6.

followed by ethics advice, and that obtaining written informed consent would be “prudent”.

197. However, Associate Professor Miles also acknowledged that a range of views may be held on whether a particular treatment is innovative or experimental, and that the “ongoing involvement of fellow [local] psychiatrists ... would suggest that [Dr A’s] peers did not share [Associate Professor Miles’] interpretation of the innovative nature” of the use of ketamine for TRD.
198. Dr A himself acknowledged that there is not a clear answer as to the point at which the level of evidence is sufficient for a treatment to cease being regarded as experimental. However, he and Dr D both advised HDC that they were confident that this point had been reached in relation to the prescription of ketamine for TRD.
199. As noted by Associate Professor Miles, the essential issue is whether there is a body of evidence that supports the treatment or procedure being safe and efficacious. I accept that at the time Dr A began prescribing ketamine there was evidence (albeit limited) of its efficacy in treating TRD, and that ketamine has been used for humans for many years for a variety of purposes. I note that the data sheet approves both IM and IV use.
200. There can be a “grey area” with no clear line between an accepted (although uncommon and off-label) treatment and an experimental treatment. On balance, however, I consider that it was open to Dr A and his colleagues to conclude that the prescribing of ketamine for TRD was not experimental. However, in my view, it was a borderline situation. In response to my provisional opinion, Dr A submitted that the failure to record his consultations with his peers was “entirely consistent with standard practice throughout New Zealand at the time” and that issues such as off-label prescribing are frequently discussed at peer group meetings in a free, frank and confidential manner. He submitted that to be required to keep a record of such discussions “may well be contrary to the quality assurance provisions of the HPCA Act”. I disagree. What I am advocating is consultation of the nature of that anticipated by the Royal Australian and New Zealand College of Psychiatrists Practice Guideline #4, “*The use of Medication in Dosages and indications outside normal clinical practice*”, which provides:

“Consultation with an experienced colleague is recommended, including consideration of a formal written request for a second opinion on treatment options, prior to commencing treatment. Documentation of the evidence that substantiates the new treatment plan will help to support the decision.”

201. There is no reason why documentation of such consultation should be problematic. Rather, it provides useful clarification that the relevant issues have been considered and discussed.
202. Despite Dr A’s submission, I remain of the view that in the circumstances, Dr A should have recognised the tension between an accepted (although uncommon and off-label) treatment and an experimental treatment and acted in a more precautionary

manner by carefully recording his consultation with his colleagues, and his consideration of the factors in the practice guidelines. In addition, the more prudent course of action would have been to have consulted with the DHB management, provided full written information to all patients (including information on the off-label nature of the prescribing) and obtained written consent from all patients.

203. Furthermore, it would have been appropriate for Dr A to have acknowledged and responded to the concern that his prescribing of ketamine might have been perceived as an experimental procedure when the concerns were first raised with him.

Conclusion: Not research or an experimental procedure

204. Given that Dr A had already expressed an interest in researching the optimal dosage of ketamine for treating TRD and presented his findings to his peers, it is not surprising that there was a view that he was conducting research. However, taking into account the nature and history of the patients concerned, and that the primary purpose of the prescribing was to treat patients suffering from TRD, I do not consider that Dr A was undertaking research. While finely balanced, I am also not satisfied that his prescribing of ketamine amounted to an experimental procedure given the existing (albeit limited) evidence of the efficacy of ketamine in treating TRD, and its known safety when used in humans, for example, in anaesthesia and pain relief.

Off-label prescribing and compliance with relevant practice guidelines

“Off-label” prescribing

205. The use of ketamine to treat TRD involved the prescription of an approved medicine for an unapproved indication and was, therefore, off-label prescribing.
206. The first six patients gave verbal agreement to have the treatment after having had information about ketamine provided by medical staff. The DHB stated that all patients were provided with written information; however, I note that this was not always recorded, and that some patient notes are unclear as to when the written material was provided.
207. Dr A said that he thought he talked to patients about the use of ketamine to treat TRD being an unapproved use, but did not necessarily use the term “off label”. This was also the evidence of others involved in, or who witnessed, the informed consent process.
208. The Royal Australian and New Zealand College of Psychiatrists Practice Guideline #4, *“The use of Medication in Dosages and indications outside normal clinical practice”*, requires the following conditions to have been met before prescribing unapproved treatments:
- Standard treatments have failed or are considered inappropriate.
 - Documentation of the reasons that require the non-standard treatment, along with a thorough assessment of the patient’s diagnosis and clinical state.
 - Consultation with an experienced colleague.
 - Relevant monitoring undertaken and recorded.

- Informed consent obtained and recorded.
 - An end point decided, discussed with the patient, and documented.
209. Similar requirements are set out in the New Zealand Medical Association Code of Ethics.
210. It is accepted that standard treatments had been unsuccessful in treating the depression suffered by these patients, the reasons for treatment and the patients' assessments were recorded and, although written consent was not always obtained, informed consent was obtained and recorded. While, from the documentation, it is not clear to what extent the earlier patients were aware that the use of ketamine was an off-label use, I consider it more likely than not that this concept was communicated to the patients even if the term "off label" was not always used.
211. Associate Professor Miles noted his concern that the patients may have been vulnerable and potentially influenced by the hope offered by ketamine treatment, and so discounted the minimal evidence regarding efficacy and the fact that this was an unapproved use of ketamine. None of the patients interviewed by my staff raised any concerns about this issue. There is also no clinical evidence before me that any of the patients were not competent to consent to the treatment. Furthermore, I have received no evidence that patients were put under any pressure to consent.
212. I note the comments of Dr Fraser that Dr A monitored the effects of the ketamine treatment and collected appropriate data to allow evaluation of those effects. Such monitoring and data collection allowed Dr A to meet the monitoring and recording requirement set out above, given ketamine was being prescribed off label.
213. I accept that in the course of treating patients it is inevitable that a health provider will collect "data", and that this is a necessary part of clinical practice. This may relate to the efficacy or side effects of a medication or other intervention and does not indicate that research is being conducted.
214. I accept that Dr A discussed the proposed administration of ketamine with his local peer group before he commenced using it. However, these discussions were not formalised or recorded. In my view, it would have been prudent to have done so in so far as the discussion related to the proposed administration of ketamine.
215. With regard to the determination of an end point, Dr A advised that consent was obtained for a single injection of ketamine. He said that if the patient failed to respond, it was not appropriate to administer further ketamine to that person. Thus in those cases the end point was the failure to respond.
216. In some cases where there was limited response, the dosage was increased. In others, the beneficial effect was short-lived, and further injections followed. Dr A stated that the full informed consent process took place before the first administration and was not repeated before subsequent injections were administered. I note that two patients have sought ongoing treatment with ketamine because of the ongoing benefits they have experienced. It appears that the end point for patients receiving ongoing

treatment was either when the treatment was no longer beneficial or when the patient no longer wished to be treated with ketamine. In those cases Dr A should have discussed and recorded the anticipated end point.

217. I accept that, overall, Dr A complied with the Royal Australian and New Zealand College of Psychiatrists Practice Guideline: “*The use of Medication in Dosages and indications outside normal clinical practice*”. However, as stated, this was a situation where the fact that peer discussions about the extant literature had occurred should have been recorded. Furthermore, more explicit documentation regarding the discussion of the fact that this was off-label prescribing, and the anticipated end point of the treatment, should have occurred for all patients. It is not recorded in all cases that written information was provided to patients.

Conclusions

218. The controversy surrounding these events demonstrates that different minds may form different views as to whether or not a particular treatment amounts to research, or is experimental. Dr A formed the view that the extant research provided a sufficient base on which to treat patients with ketamine. That position was not unreasonable, and was thus open to him. I do not doubt that Dr A’s research interests in this area informed his use of ketamine in Ward X. There is nothing unusual or inappropriate in that. However, given Dr A’s known research interest in ketamine and its use in treating depression, it was not beyond the realms of possibility that Dr A’s treatment of patients in Ward X with ketamine would raise questions as to whether or not research was being undertaken.
219. In my view, Dr A should have acted more formally in the process leading up to the use of ketamine on Ward X. He had a particular interest in the use of ketamine in treating depression and in developing research to explore that. While treating the patients in Ward X, he was in the process of developing a trial in the use of ketamine for treating depression in cancer patients on another ward. I expect that in the future Dr A and his colleagues will adopt a more disciplined approach to the recording that consultations with peers has occurred when approaching the question of whether a treatment also constitutes research or is an experimental treatment.
220. While I consider it goes too far to suggest there was ambiguity in Dr A’s actions, I do consider there was insufficient formality in relation to what was clearly an uncommon approach to treatment of patients with TRD. I consider that aspects of the record-keeping processes adopted should have been better, as could the attention to detail in Dr A’s abstract and presentation.
221. For the reasons outlined in paragraphs 182–189, I am satisfied that the evidence does not, on the balance of probabilities, support a finding that research was being undertaken. For the reasons outlined in paragraphs 192–203, I am also satisfied that the evidence does not, on the balance of probabilities, support a finding that the treatment, although uncommon, was experimental.

Opinion: Southern DHB — Adverse comment

222. It is important that innovation is able to flourish in the health and disability sectors. However, it is even more important that consumers are fully engaged in their treatment, fully informed as to their options and choices, and properly consent to their treatment course. I am satisfied that in this case the patients were provided with the information they needed, and that the decisions they made were made on an informed basis.
223. However, in April 2010 when Dr A began using ketamine in Ward X, there was no requirement that he advise the DHB of his intentions. I note that Dr D considers that Dr A is very experienced in the field of psychopharmacology and stated that he would defer to Dr A with regard to prescribing and the use of ketamine.
224. Dr D said that it would not be usual for him to seek information about the prescribing habits of vocationally registered psychiatrists employed by the DHB; however, I do not consider that this prescribing was routine. As ketamine had not been used previously to treat TRD in any New Zealand DHB, it should have been viewed as unusual. The DHB should have had in place a requirement that management be informed about the proposed prescribing of medications in such circumstances. In my view, it was suboptimal for the DHB to adopt such a “hands off” approach to overseeing the clinical activities of its staff.
225. Furthermore, in contrast to a number of other DHBs, at the time of these events the DHB did not have a policy in place regarding off-label prescribing. In 2012, Southern DHB made some attempt to fill that gap. The policy that has subsequently been developed by the DHB requires that when prescribing an approved medicine for an unapproved indication in the absence of evidence from “well conducted trials”, the SMO must consult with at least one other SMO colleague and document the outcome in the patient record, and obtain written patient consent.¹⁹ As is clear from this case, there are differing opinions as to what amounts to evidence from “well conducted clinical trials”, and it is unclear what the requirement imposed by the policy means in practice. In addition, the point at which the concurrence from peer consultation is sufficiently positive is uncertain. Furthermore, Dr A has submitted that if such consultation takes place during peer group meetings it is inappropriate to maintain any record of the discussions. Accordingly, I consider that the policy developed by the DHB is not sufficiently specific to make the DHB’s expectations clear, such as, for example, the circumstances in which clinical review is required.
226. Dr A discussed the use of ketamine for treating TRD with his peer group, before he started prescribing it on Ward X. However, given the context, the counsel of prudence would have been to formally record his consultations with his peers and in particular any expressed concerns. The DHB should have had a procedure in place that requires such documentation.

¹⁹ Finalised on 19 January 2012.

227. Additionally, I consider that the DHB should ensure that it has policies that make clear requirements and reporting expectations where the distinction between research and treatment is at risk of becoming (or being seen to be becoming) blurred.
228. Finally, with regard to the question posed by the National Health Board: “Did the DHB mislead the HDC via the information provided in response to HDC questions?” As stated in paragraphs 37–45, I sought clarification of the information provided and I am satisfied that Southern DHB did not mislead HDC.
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Other comment

229. As part of his response to the provisional opinion, Dr A produced a submission from a senior representative of a School of Medicine, addressing the suggestion that Dr A should maintain an appropriate separation of his academic and clinical roles. The School of Medicine representative advised that the current Joint Clinical individual agreement was created in the 1990s in order to “reflect the complex arrangements that allow clinical academics to function”. The School of Medicine representative considers that service provision, teaching and research are integral parts of a clinical academic’s role, and “the bulk of a clinical academic’s working life is spent in activities that integrate two or more of these functions”.
230. The School of Medicine representative advised that a considerable amount of work has been undertaken to try to describe the multiple ways that DHBs and the Faculty share staff and the roles involved. He said that “the fact that to this point agreements have not been reached reflects the complexity of the situation”.
231. It is clear that this is not a new issue. I accept that the integration of treatment, teaching and research can be ultimately beneficial to patients and to the public generally. Furthermore, many clinicians will at some point develop research interests that they wish to pursue. The essential issue is that they be clear when these activities overlap, both in their own thinking and in their communications with patients.
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Recommendations

232. I recommend that

Southern DHB:

1. review its current policy on off-label prescribing, including whether clinicians have a common understanding of what is meant by “well conducted clinical trials”, the meaning of innovative treatment, what precautions should be taken, what peer review is expected, how it should be recorded, at what point the concurrence from peer consultation is sufficiently positive, and what ethical

consideration needs to occur with different levels of novel or unusual medications;

2. ensure they have in place policies and protocols that assist staff to determine whether or not proposed prescribing falls in the “grey area” of uncertainty between common off-label use and experimental treatment. These policies and protocols should provide guidance to staff regarding the action they should take in situations where there is any doubt about the current acceptability of any particular prescribing, for example, the requirements for consultation with peers and/or ethics committee review, compliance with Medsafe guidelines, communication with DHB management, and adequate recording of the compliance with the policies and protocols;
3. ensure they have in place policies and protocols that set out what is required of staff members in relation to their clinical and research activities (including the responsibility to exercise caution in situations where these activities may overlap), and the related reporting and review requirements;
4. provide copies of the above policies to the National Health Board by **30 September 2013**; and
5. audit compliance with the policies to ensure their effectiveness and that clinicians have similar understandings of their application, and report to HDC on the outcome of the audit by **30 June 2014**.

Dr A:

6. ensure that consultations with peers about off-label treatments are recorded, including any dissenting opinions expressed and details of the literature considered;
7. develop a process he will use to ensure that all elements of the College of Psychiatrists’ Practice Guidelines are considered and recorded when using off-label treatments;
8. arrange for this process to be reviewed by a clinician approved by the Royal Australian and New Zealand College of Psychiatrists and provide a report from the reviewer to HDC by **30 August 2013**.

All other District Health Boards:

9. ensure they have in place appropriate policies on off-label prescribing;
10. ensure they have in place policies and protocols that assist staff to determine whether or not proposed prescribing falls in the “grey area” of uncertainty between common off-label use and experimental treatment. These policies and protocols should provide guidance to staff regarding the action they should take in situations where there is any doubt about the current acceptability of any particular prescribing, for example, the requirements for consultation with peers

and/or ethics committee review, compliance with Medsafe guidelines, communication with DHB management, and adequate recording of the compliance with the policies and protocols;

11. ensure they have in place policies and protocols that set out what is required of staff members in relation to their clinical and research activities (including the responsibility to exercise caution in situations where these activities may overlap), and the related reporting and review requirements; and
12. provide copies of the above policies to the National Health Board by **30 September 2013**.

National Health Board:

13. review the policies from the DHBs, assess the policies for consistency and efficacy, and report to HDC by **31 March 2014**.

Follow-up actions

- A copy of this report with details identifying the parties removed, except the experts who advised on this case and Southern DHB, will be sent to the Medical Council of New Zealand, and it will be advised of Dr A's name.
- A copy of this report with details identifying the parties removed, except the experts who advised on this case and Southern DHB, will be sent to the Royal Australian and New Zealand College of Psychiatrists, the National Health Board (Ministry of Health), and all other DHBs.
- A copy of this report with details identifying the parties removed, except the experts who advised on this case and Southern DHB, will be placed on the Health and Disability Commissioner website, www.hdc.org.nz, for educational purposes.

Appendix A: Independent expert advice to the Commissioner — Dr Allen Fraser

REPORT TO THE HEALTH AND DISABILITY COMMISSIONER

INTRODUCTION

At the request of the Commissioner I am providing an opinion on case number 11/01072. In doing so, I am abiding by the Commissioner's Guidelines for Independent Advisers, which I have read.

I am a specialist adult general psychiatrist, trained mainly in Auckland, with time at St Thomas' Hospital in London. My specialist qualifications are DPM (Otago, 1973), MRCPsych (1976) and M/FRANZCP (1978/1981). I also completed the requirements for the Diploma of Professional Ethics (1998).

I have extensive experience in inpatient acute psychiatry and also in outpatient care, including provision of an acute day hospital service. My main research interest has been in the major mood disorders, and since retiring from the public sector my clinical practice has concentrated on the assessment and treatment of patients with bipolar disorder, and major depressive disorder, especially treatment resistant depression.

The Commissioner has asked for advice to assist in his consideration of the following:

The appropriateness of services provided by Southern DHB to patients receiving ketamine on [Ward X], [the public hospital] in 2010 and 2011.

The adequacy of information provided by Southern DHB to patients receiving ketamine on [Ward X], [the public hospital], including the informed consent process.

The appropriateness of services provided by Dr A to patients receiving ketamine on [Ward X], [the public hospital] in 2010 and 2011.

The adequacy of information provided by Dr A to patients receiving ketamine on [Ward X], [the public hospital], including the informed consent process.

The Commissioner provided extensive supporting information

- A Initial complaint letter from Mr B, dated 03 December 2010
- B Supporting information and correspondence from [Mr B]
- C Initial HDC request for a response sent to [Dr A], dated 09 February 2011
- D Initial response by Southern DHB, dated 04 March 2011 (with appendices)
- E HDC correspondence to the parties, dated 15 April 2011
- F Letter from [Mr B] to HDC, dated 24 May 2011
- G HDC letter to Southern DHB and [Dr A], dated 07 July 2011
- H SDHB response, dated 26 July 2011 (with appendices)
- I HDC letters to [Dr A] and SDHB, dated 01 September 2011

- J Email correspondence from [Mr B], received 21 July 2011
- K Referral letter from the National Health Board to HDC, dated [...]
- L HDC correspondence to parties notifying intention to investigate, [date]
- M Detailed response from SDHB to HDC, dated [...] (with appendices)
- N Letter from SDHB dated [...]
- O National Health Board letter to HDC, dated [...]
- P Further response from SDHB, dated [...] (with appendices)
- Q Email [...] providing a screenshot copy of the creation date details of the electronic word document “Information-consent sheet ketamine in depression.doc”
- R Information from [Dr D], dated [...]

BRIEF FACTUAL SUMMARY

Based on information in the documents provided to me, commencing in April 2010, [Dr A] treated with ketamine injections a number of patients suffering from treatment-resistant depression. [Mr B] became aware of this in May 2010 and sought information and clarification about a number of matters from [Dr A], Southern District Health Board, and [the university]. Dissatisfied with the responses he was given, he lodged a complaint with the Commissioner in December 2010.

The main thrust of [Mr B’s] complaint was that [Dr A] was undertaking a research project, that he had not gained Ethics Committee approval for this, and in so doing he had infringed patients’ rights. The first patients treated with intramuscular injections of ketamine were not asked to sign a consent form. The extracts from the clinical notes which were made available to me, documented that there had been a discussion with each patient about the use of ketamine, and further documented that the patient had given verbal consent to the injections. These patients were treated between 19 April 2010 and 13 September 2010.

On 20 September 2010 the *Information-consent sheet ketamine in depression* form was created. All patients subsequently treated with intramuscular injections of ketamine for depression, signed this form, which included statements that that they had “read [the] information sheet”, that they had “had a chance to discuss any questions”, and that they agreed “to have a ketamine injection for [their] depression”.

In April 2011, the form was modified by the inclusion of a sentence to the effect that the use of ketamine in this way is what is termed “off-label”. Before the form was modified, that the treatment was off-label was included as a handwritten note on some of the forms.

[Dr A] and SDHB deny that the treatment of these patients was part of a research project. On 21 December 2010 the [Ethics Committee] approved a research proposal by [Dr A] for the use of ketamine injections in terminally ill patients with cancer.

When the Commissioner informed Southern DHB of the investigation, [a senior DHB medical manager] banned further prescribing of ketamine for psychiatric disorders. Two patients who had been receiving ongoing injections of ketamine to prevent

relapse, asked to be allowed to continue with the treatment. After being given an explanation about what [Dr D] called “*the controversy surrounding [Dr A’s] off-label prescribing of ketamine*”, both signed a consent form to continue receiving the treatment.

ADVICE REQUIRED BY THE COMMISSIONER

1. *With reference to relevant literature, standards, and guidelines where appropriate, please clarify what constitutes the following, and the clinical context in which these terms are normally used:*

A clinical trial/clinical research

Experimental prescribing/treatment

“Off label” or “novel” prescribing/treatment

The first point to make is that the word “trial” can have two meanings in this context. One meaning is synonymous with experimental treatment. It also tends to be synonymous with one form of clinical research. This is usually the meaning which applies when the clinician does not have certainty about what is the best treatment, and is undertaking a study to try and clarify that. A clinical trial of this nature potentially exposes the patient/subject to a treatment which may not benefit that individual directly.

Wells (1999) stated that “The gold standard for obtaining information on how psychiatric treatments affect health has been the randomized controlled clinical trial”. Such trials evaluate efficacy; whether or not the treatment being studied improves outcomes.

The second meaning is a “test”. Used in this way the treatment is being given to a person to see if that particular person will benefit from the treatment. Clinicians not infrequently talk about a “*trial of treatment with ...*”. This indicates two things; firstly that the patient has not previously had this (or similar) treatment before, and secondly that the treatment is known to not work for every patient and/or may not be tolerated by this patient (this applies to most treatments).

Clinical research may describe the sort of clinical trial described above; a randomised controlled clinical trial. This pertains when there is a state of uncertainty regarding the comparative therapeutic merits of the experimental and the control treatments (Freedman, 1987). The use of a placebo arm in a study is relatively common, especially in psychiatry. This can raise concerns when there are accepted treatments which are known to be effective.

Whether or not there is a placebo control, the experimental treatment is of unknown efficacy, and the patient/subject runs the risk of being exposed to treatment which is inefficacious, whether that is the treatment being studied, or a placebo treatment. Because of this, any such research (or trial) requires ethical examination, and approval.

However, clinical research may be of a quite different nature. A clinician may wish to examine the results of an accepted treatment in his/her particular setting. Data will be collected as part of the treatment of patients, and then examined to determine any of a number of issues. For example, whether the particular patient group is responding as well as those reported on in the literature, or whether the clinician's use of the treatment is meeting best practice standards and outcomes.

Experimental prescribing or treatment suggests that there is no clear opinion held by the clinician as to what is the likely outcome. Such prescribing/treatment may occur in research studies, which would need ethical approval. It may also occur when the patient has failed to respond to any other interventions, and there may be some reason for believing that the experimental treatment could benefit the patient.

“Off label” prescribing means that within the jurisdiction in which the clinician is practicing, the medication being prescribed is not registered for the use to which the clinician is putting it. In some circumstances this reflects nothing more than that the manufacturers of the medication have chosen to not seek registration for that use of the medication in that jurisdiction. It does not mean that there is no evidence for its use in that particular way. Indeed in some situations, there is significant evidence available.

At times, off-label prescribing may be used to describe prescription of a medication where there is either inconsistent evidence, or even no evidence to support the prescription of the medication in the particular indication. Description of a particular treatment as “novel” suggests the absence of studies on this treatment in this condition. It would be expected in such circumstances that the clinician would have a theoretical justification for the particular novel prescribing/treatment.

Excluding the use of the word “trial” used to mean trying a treatment to see if it works in an individual, a clinical trial and clinical research require that there is a research protocol, ethics committee approval, and informed consent by the patient/subject. Truly experimental prescribing would fall into such research. Off-label prescribing differs considerably from research; although the medication may not be registered for the particular indication, there is evidence to support the prescription. Such off-label prescribing may be rare amongst one's colleagues, or it may be very common; a recent report from Christchurch showed that over 90% of clinicians prescribe quetiapine “off-label” (Monaterio and McKean, 2012). This type of off-label prescribing does require that patients are appropriately informed, but such use is neither experimental nor research.

2. In your view, do the following categories accurately represent the situation that exists in New Zealand in relation to medical practitioners' prescribing options? Please comment.

Prescribing of approved medicines for approved indications

Prescribing of approved medicines for unapproved indications (where there is substantial evidence that the medication has accepted efficacy and safety in the treatment of the indication)

Prescribing of approved medications for unapproved indications (where the evidence base for the safety and efficacy of prescribing is not extensive and where use of the medicine for that indication is not common)

Use of experimental medicines.

Medsafe has provided information (<http://www.medsafe.govt.nz/profs/Riss/unapp.asp>) on prescribing in these circumstances, for health professionals. As is pointed out in the introduction, a registered medical practitioner may prescribe medication whether or not it is approved, and whether or not its use is approved for the particular condition.

Prescribing of approved medicines for approved indications (a registered antidepressant for the treatment of depression) is standard practice. Medical practitioners may also prescribe approved medicines for unapproved conditions, and the evidence base to support the use in the unapproved indications can vary from minimal to extensive. It is good practice to inform the patient of the absence of approval, and of the nature and extent of the evidence. The less extensive the evidence, the more appropriate it is to obtain written consent.

I agree that medical practitioners are permitted to prescribe “experimental medicines”. An experimental medicine would typically be a medication which has not been approved because there is insufficient evidence to support either efficacy or safety or both. It is important to distinguish that situation from experimental use of an approved or unapproved medication where evidence is lacking in the indication for which the clinician is prescribing it; then the use might be experimental, rather than the medication.

3. What, in your understanding, are the approved clinical indications and uses for ketamine in New Zealand?

Ketamine infusion is approved for intravenous use, either as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, or for the induction of anaesthesia prior to the administration of other general anaesthetic agents, or to supplement low-potency agents, such as nitrous oxide.

4. In your view, is the current evidence base for the use of ketamine for treatment resistant depression adequate or sufficient to support off-label prescribing?

I am aware of three reports of double blind controlled trials of the use of intravenous ketamine infusions for treatment-resistant depression. All three reports have come from the one team, at the Experimental Therapeutics & Pathophysiology Branch, National Institute of Mental Health, in Bethesda, Maryland, United States of America (Zarate et al, 2006; Diazgranados et al, 2010; Zarate et al 2012).

Unusually for research on depression, two of these three reports involved the treatment of bipolar depression. The 2012 paper was a small replication study (15 patients) of the study reported in 2010 by Diazgranados et al. That study was also small (18 patients). The 2006 report in unipolar depression was likewise small with just 18 subjects.

It is not surprising that the numbers involved in these studies are small. Treatment resistant depression was defined in Zarate et al (2006) as having “*failed at least 2 adequate antidepressant trials*”, and to be still at least moderately severely depressed. The group’s initial study in bipolar depression likewise required two failed trials of treatment; one with optimal doses of mood stabiliser (standard approach to treating bipolar depression), and one antidepressant trial. It took three years to get 18 patients for this study.

In addition, there have been a number of case reports and open studies of small size.

In a review, Mathew et al, 2012, noted that there have been few double blind controlled studies, and they further commented that little of the experience with ketamine has been outside of research settings. A second review (Covvey et al, 2012) reached a similar conclusion; that ketamine for treatment resistant major depressive disorder requires further evaluation.

The overall impression gained from the published data is, however, that ketamine (almost always given by intravenous infusion) can have a substantial effect on reducing depressive symptoms in many patients. Having said that, I have one major concern about almost all the published papers. This is the measuring of response. Response has mostly been measured using the Montgomery and Asberg Depression Rating Scale. This is a well validated measure of depression and is generally regarded as being sensitive to change. My concern is not the scale itself; it is the way in which the scale has been used. The ten items in the scale are to be rated on the basis of symptoms experienced over the past week. The scale is not designed to accurately measure changes in mood state and symptoms occurring within minutes or hours of an intervention, or even within days, although that may be a little more justified. As some of the reports are showing loss of benefit by a week after the infusion, the use of the Montgomery and Asberg scale in this unconventional way, may have resulted in the response to ketamine being reported as more positive than had some other measure of short term change been used. Nevertheless, on the basis that treatment resistant depression, by definition, is not responsive to standard treatments, I believe that the published literature is positive enough to justify off-label prescribing of ketamine for patients with a treatment resistant Major Depressive Episode.

5. In your view, is there sufficient current evidence that ketamine is a safe and efficacious treatment for treatment-resistant depression?

I believe that the current evidence supports that while there are some unwanted effects from ketamine, more marked with larger doses and with intravenous infusions, that ketamine is a safe treatment for treatment-resistant depression, when given in an appropriate clinical setting. The published evidence to date suggests that ketamine is efficacious in producing positive changes in mood state in many patients with treatment-resistant depression. The duration of those effects can be short, and the method of measuring the changes leaves a lot to be desired. Nevertheless, there is now an accumulated body of evidence pointing towards a positive effect in the treatment of treatment-resistant depression.

6. *In your view, is there any distinction between “routine” and “less common” off-label prescribing?*

What may be called “routine” off-label prescribing is usually off-label as a result of the particular indication for a medication not being approved within New Zealand. There is not infrequently significant evidence in favour of the practice, and in some cases, other countries have approved the indication. The less evidence there is for an indication, the less commonly will medical practitioners prescribe off-label. This is certainly one way in which these types of prescribing differ. However, it would be expected that a doctor who prescribes medication off-label, is doing so on the basis of awareness of evidence to justify it, whatever is the amount of that evidence. In that, there should be no difference.

In both situations, the medical practitioner would be expected to ensure that the patient is aware that the use of the medication is off-label, ensuring that the patient is fully aware of what that means. The less common that the particular prescribing is amongst one’s peers, the more necessary it will be to ensure that informed consent to the treatment (which should be gained for all treatments) is well documented, including signed written consent where appropriate.

7. *Please provide any comments you have in relation to [Dr A’s] prescribing of ketamine for treatment-resistant depression in patients on [Ward X] and his clinical trial relating to the use of ketamine for cancer patients.*

I have seen parts of the files of the patients who were treated by [Dr A] and his team. The parts of the files made available informed me as the reader that the patients had had the treatment explained to them and that consent to be treated with intramuscular ketamine was obtained by [Dr A]. There is also information about changes in the scores on the rating scales, and notes about unwanted effects.

I take on face value that the diagnosis of treatment resistance was established in all cases, as I have no reason to doubt that. Although there is a variety of what may be termed primary diagnoses, all patients were recorded as suffering from a major depressive episode at the time of the treatment with ketamine.

In a number of cases, there is evidence in the notes of concern about failure to respond, and about suicidal thinking and/or behaviour. The literature on ketamine contains reports of rapid loss of suicidal thinking, and also (allowing for my caveats about the way this was measured) rapid decrease in severity of depressive symptoms. For these reasons, I believe that [Dr A] was justified in considering the use of ketamine.

He did alter the route of administration of ketamine from that reported in the literature. Apart from two reports of ketamine being given orally, all others that I have read used ketamine intravenously. [Dr A] developed a protocol for intramuscular administration.

Intravenous administration has some advantages when the ketamine is given as a slow infusion. There can be closer control of the amount that is given dependent on the

occurrence and severity of unwanted effects. There is substantial experience in anaesthetics and treatment of pain with intravenous administration. There are also disadvantages, as the incidence of unwanted effects such as some blood pressure changes, and the occurrence of brief dissociative states, is greater.

With his acknowledged expertise in psychopharmacology, [Dr A] might be expected to have made an appropriate decision to change the route of administration, presumably taking into account bioavailability. From the file extracts I read, his decision would appear to be supported, as unwanted effects were few and relatively mild.

The patients were not invited to participate in a research study, because this was not research in that sense. As I would expect of any clinician prescribing off-label in this way, [Dr A] monitored the effects of the treatment, and collected data to allow evaluation of what were the effects of the treatment. This should be seen as a form of clinical audit rather than clinical research. Failure to have done so would attract strenuous criticism, as he would have not had objective data to evaluate the treatment.

[Dr A's] planned trial of the use of ketamine for depressed terminally ill patients with cancer is significantly different from the use of ketamine in [Ward X]. The basis for undertaking such a trial is clearly established by the literature on ketamine in depression, and the literature on ketamine in the treatment of pain states. Terminally ill cancer patients often suffer considerably from pain and also from depression. Standard antidepressant treatments take time to work, and often are not greatly helpful in this setting.

There are thus good and sensible reasons for proposing to treat such patients with ketamine. The choice of intramuscular rather than intravenous administration is also well justified as patients in this situation not infrequently have difficult venous access.

A formal research study in this situation is required by the absence of any significant literature on such use of ketamine. The research question posed by this research (is it possible to relieve the distress caused these patients by depression and pain) is an important one, and is answerable by the research I understand he is to conduct.

8. What is your understanding of the expected risks, side effects, and benefits of ketamine for treatment-resistant depression?

The use of ketamine is contraindicated in any patient for whom significant elevation of blood pressure would be hazardous. Cardiac function should be monitored after the administration of ketamine, and for a few hours.

Because it is an anaesthetic agent it is possible, although highly unlikely, that when ketamine is used in the treatment of treatment-resistant depression there may be impairment of consciousness, and/or respiratory depression. There would need to be awareness of that and resuscitation equipment available.

Psychological unwanted effects include dizziness (or feeling light headed), hallucinations, nightmares, vivid imagery, and delirium. The latter may be more common if the patient abuses alcohol. These effects are typically brief, especially in the doses used in treatment-resistant depression. Long term psychiatric ill effects are not reported. Ketamine is a drug of abuse, and has recently been reported to be being used at an increasing frequency in New Zealand.

Because benzodiazepines may prolong the effect of ketamine, extra caution would be needed if a patient with treatment-resistant depression is taking benzodiazepines.

The benefits of ketamine in treatment-resistant depression are that it is reportedly associated with a rapid improvement in mood (after resolution of any psychological unwanted effects), and especially with a rapid loss of suicidal thinking and urges. Unfortunately, the majority of responders lose the improvements within 7–14 days, although improvement may persist for longer; one patient was reported as remaining in full remission for more than 15 months with maintenance treatment with ketamine every three weeks.

9. In your view, based on the clinical records available, was each of the 11 patients highlighted by this matter clinically indicated for ketamine use in treatment-resistant depression, and competent to consent?

The clinical records available (incomplete extracts) do not provide adequate information to make definitive comments about these issues in all cases.

The available information for four of the eleven patients does not contain any diagnostic statement, nor is there sufficient information to do more than state that the patients were observed to have depressive type symptoms and behaviours while on the ward. Diagnoses mentioned in the other cases included Bipolar II Disorder, Major Depressive Disorder, and Borderline Personality Disorder. When Borderline Personality Disorder was mentioned, the patient was also identified as being severely depressed as well.

The scores on the Montgomery Asberg Depression Rating Scale were in the moderately severe to severe range. Suicidal ideation, and at times behaviour, was common. Marked distress at how the person was feeling was commonly noted. A number of files noted multiple previous medication trials without benefit.

On the basis of the information available (with the caveat that it was incomplete, and patchy), it appears that these patients would have met criteria for treatment-resistant depression. It would have been better had there been a clear statement to that effect in the notes at the time the decision to recommend ketamine was documented.

The patients often had significant complicating factors, which would have lessened the likelihood of response to treatment. These included Borderline Personality Disorder, and one patient positive for HIV. Chronic self harm was also an issue. It is not uncommon that clinicians are more inclined to try different treatments in

situations where standard treatments have not worked, and where there are complicating factors.

In my opinion, the decision to offer each of these patients treatment with ketamine was clinically indicated, as alternative treatments had been tried without success.

There is nothing in the notes available to me that would suggest that any of these patients lacked the competence to consent to the treatment. In only a minority of the files was there sufficient information to allow a positive assessment that the person was probably competent to consent. Likewise, only a minority of files contained a clear statement that the patient understood the treatment and the likely benefits and unwanted effects.

I do not consider that the notes available to me allow a definitive statement about competence of the patients at the time of giving consent to treatment with ketamine. Based on my experience in an acute ward setting I would assume that these patients were highly probable to have been competent.

10. Please comment on the nature of the consent process that you and your peers would expect to eventuate in each of the prescribing scenarios outlined in Question 2.

Good clinical practice expects that a medical practitioner informs every patient of appropriate treatment options, and also ensures that the patient is aware of and understands the reasons for treatment, the intended benefits and the likely unwanted effects, including any significant (especially for that person) risks. In most circumstances, oral agreement is deemed all that is necessary for the first scenario in Question 2.

The second scenario carries the additional responsibility that the clinician should inform the patient that the proposed use of the medication is for an unapproved condition. That would necessitate that the clinician explain what is meant by “*unapproved condition*”. In the most usual circumstances under scenario 2, the clinician should be able to inform the patient that the condition not being approved does not mean that it is inappropriate prescribing. Oral agreement with the proposed treatment would be all that would be expected. This should be clearly documented in the notes.

The third scenario raises the level of information required to be given. In circumstances such as this scenario imagines, the clinician should have available written information about the use of the medication in such circumstances, assuming that there is such information. The clinician should explain carefully why he or she is using the medication in this way, and be prepared to allow the patient ample time to consider the proposed treatment. As well as documenting the process of informing the patient, and the patient’s agreement, written consent would be expected if the proposed use of the medication is substantially outside usual practice, and the evidence for the use is minimal and/or inconsistent.

The fourth scenario (the use of experimental medicines) is outside ordinary clinical practice and would require formal research proposals, and ethical committee approval. The consent process required would be established by the ethics committee, and would be expected to include full information about the medication, the risks and the possible benefits. Additionally, it would be expected that the patient/subject would be made fully aware that the purpose of the study is to gather group knowledge. Consent would have to be in writing.

11. *In your view, does [Dr A's] prescribing of ketamine for treatment-resistant depression in this case fall into any of the above categories outlined in question 2? Please comment.*

[Dr A's] prescription and administration of ketamine in these 11 cases is clearly the use of an approved medication for an unapproved condition. Because, as I understand it, ketamine has not been approved for this use in any jurisdiction, I consider that [Dr A's] use falls into the third scenario; prescription of an approved medicine for an unapproved indication where use in that condition is not common. The evidence base for the use of ketamine in treatment-resistant depression is not extensive. It is however, reasonably consistent in the reported findings.

12. *Based on the information provided, please provide your overview of the appropriateness of [Dr A's] prescribing of ketamine to treat patients with treatment-resistant depression in [Ward X] of [the public hospital] in 2010 and 2011.*

The management of treatment resistance in depression is complex and difficult. There have been a number of attempts to define what is meant by treatment resistance. Treatment resistance has been considered to fall into five stages (Thase and Rush, 1997), where Stage I is failure to respond to at least one trial of one major class of antidepressant, and Stage V is failure to respond to an adequate trial of all major classes of antidepressant and also failed to respond to ECT.

The definition of treatment resistance adopted in the majority of the reports I have read of the use of ketamine, is at no more than Stage II; failure to respond to an adequate trial of at least two antidepressants in two different classes. Because most of the reports did not specify that the patients had received antidepressants from more than one class, some patients may have been at Stage I treatment resistance, according to Thase and Rush's system.

Few of the patient record extracts I have been provided with give clear information about the number of different treatments to which the patients had failed to respond. Those that did, place the patients at Stage III (at least three different classes of antidepressant one of which was a tricyclic antidepressant). At least one patient treated by [Dr A] had also failed to respond to ECT (Stage V).

Thase and Rush discuss the strategies for managing treatment resistance, and reflect the prevailing view that the more failed trials of treatment the less likely the person is to respond. That was shown very clearly by a study reported by Dunner et al (2006). This study reported on the outcomes over a two year period for 124 patients with treatment resistant depression. These patients had mostly failed to respond to at least

three different antidepressants, and had been depressed for long periods of time. The patients were treated by the clinicians, as the clinician chose; what was termed treatment as usual.

At 12 months the response rate (at least 50% reduction in severity of depression) was just 11.6%, and the remission rate was only 3.6%. Although there were more responders at 24 months (18.4%) eight of the 13 responders at 12 months were no longer responders at two years. Remission had also increased slightly to 7.8% by two years, with only one of the four 12 month remitters remaining in remission during the second year. Treatment as usual is therefore unlikely to benefit many patients with treatment resistant depression.

It is therefore appropriate for the clinician who is faced with a patient with significant treatment resistance to standard treatments, to consider every option to help the patient. Dunner et al included an assessment of social functioning in their study, and this showed significantly poor quality of life. Doing nothing is not an option for the clinician who wishes to benefit her or his patient.

The strategies available to the thoughtful clinician when a patient is at Stage III resistance and above include the use of a monoamine oxidase inhibitor (MAO Inhibitor), which is uncommon in ordinary clinical practice. Other strategies include combinations of antidepressants, and the use of augmenting medications such as a second generation antidepressant, or lithium carbonate.

I do not have available sufficient information about the medication histories of most of the 11 patients treated with ketamine by [Dr A], to know what strategies had been tried. I accept that the nature of the patients, with a high concern held by staff about self harm and suicide, would discourage the use of MAO Inhibitors, which also tend to be very poorly tolerated as a result of significant unwanted effects. There is also a risk of hypertensive crises with various foods, and other medications.

In my view, based on my understanding of the degree of treatment resistance, and other factors, [Dr A's] prescribing of ketamine (with the administration taking place in a controlled environment with monitoring) was appropriate. His attempt to assess response (using the Montgomery and Asberg Depression Rating Scale) used the scale in a way for which it was not designed. However, this was in full accord with the bulk of the published experience with ketamine use in treatment-resistant depression.

Additionally, it provided a formal process of assessment of the effects of ketamine in these patients, allowing confirmation of patient self reports and staff observations of the improvement or lack of it. That attention to monitoring the effectiveness of the treatment is commendable and what I would expect of a clinician who is prescribing an approved medication for an unapproved condition, when the evidence for doing so is not extensive.

13. If, in answering any of the above questions, you believe that [Dr A] did not provide an appropriate standard of care, please indicate your view on the severity of

his departure from that standard (and whether the provider's peers would view the conduct with mild, moderate, or severe disapproval).

In my opinion, [Dr A] adopted an uncommon treatment approach for a disorder (treatment-resistant depression) in which common approaches are singularly unsuccessful in the majority of cases. He did so with reference to the published literature, basing his information to patients on the only two reports (available at the time) of controlled trials. This treatment involved off-label prescribing of an approved medication. Treatment was given in an appropriate setting and was appropriately monitored and then evaluated.

There is evidence in the extracts from patient notes that there was discussion with the patients, and that they agreed with the proposed treatment. Consent was not in writing until September 2010, and there was not consistent indication that information was given to the patients that this use of ketamine was off-label until later in 2010. Nevertheless, informed consent was gained from every patient.

Although the initial absence of signed consent could be seen as a minor departure from the appropriate standard of care (because of the small evidence base supporting the effectiveness of ketamine in treatment-resistant depression), [Dr A's] provision of written information to patients during the consent process, balanced that, in my opinion.

Overall I believe that [Dr A] provided an appropriate standard of care.

Allen Fraser
MB ChB, DPM, MRCPsych, FRANZCP, Dip Prof Ethics
PSYCHIATRIST
28 May 2012

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Further advice

Thank you for your further enquiry on this issue. You have asked two further questions.

1. *Is there a clear consensus among clinicians and academics ... relating to the following issue:*
 - a. *At what point would the evidence regarding the safety and efficacy of a treatment transition from being considered "minimal" or "equivocal" to a point where it would be considered "sufficient" and strong enough to support, for example, off label prescribing of a particular medication for a specific clinical indication (such as off-label prescribing of ketamine for treatment-resistant depression)?*

I think that it is highly unlikely that there is consensus on when the evidence is strong enough to support a particular treatment approach. For instance, reports from Europe have shown (through meta-analysis) that the most effective strategy in treatment resistant depression (TRD) is augmentation of antidepressant medication with lithium carbonate. The evidence for the effectiveness of other approaches is less strong, yet lithium augmentation appears to be used relatively uncommonly by clinicians.

Another issue is that the published evidence for lithium augmentation for TRD suggests that about 60% of patients will respond, meaning that 40% will not. Because TRD is a difficult condition to treat successfully, and there is high morbidity and mortality, and high cost to the patient, family and society, alternative treatment strategies are wanted. Clinicians may therefore accept less rigour in studies reporting the possibility of benefit.

That becomes more likely if the treatment in question involves a well established drug which has been in use for many years, albeit for quite different indications. The safety profile of a drug such as ketamine is well enough known to offer reassurance about not doing any harm with off label treatment.

It is probable that clinicians will be more willing than "academics" to use a novel treatment for TRD, when standard approaches have not been successful, provided they feel confident about safety.

As a subsidiary question you also asked:

- b. Is this solely related to the quantity and quality of RCTs completed and peer reviewed on an issue? What other information could support the evidence base?*

In my opinion, the lack of agreement between clinicians (whether academic or non academic) on this matter is likely to be related to the issue of what constitutes evidence. The holy grail of evidence based medicine is the randomised clinical trial. There are problems with such an approach, when it excludes other forms of evidence. In 1997 Moncrieff (under the heading of Evidence-Based Psychiatry) published a critique of the literature on lithium, concluding that “*Overall there appears to be little evidence that lithium is effective ...*”, including as an adjunctive treatment in TRD. Later analyses disagreed strongly, by including other types of evidence than purely RCTs for lithium in TRD.

Case reports, clinical observations, and other forms of study can identify effectiveness of a treatment. Therefore, the relative absence of RCTs for ketamine in TRD, does not mean that there is an absence of evidence. It is true that the evidence is inconsistent and equivocal. It is equally true that the evidence for any treatment being effective in TRD is inconsistent.

There was also a third part to this question:

- c. What do you consider would be the primary reason clinicians/academics opposing the use of ketamine for TRD would cite in order to argue that the evidence base is insufficient?*

The most likely reason is that the teaching of critical appraisal ranks evidence from the highest (randomized double blind controlled clinical trials) to the lowest (expert opinion). The evidence so far available is low in that hierarchy. Therefore, the treatment is not established as being effective. Safety concerns should be allayed by the long history of the use of ketamine in anaesthesia and pain disorders.

- 2. Are you aware of ketamine having ever been prescribed for treatment resistant depression in either a hospital, community mental health, or clinical trial setting in any area of NZ other than at [the public hospital]?*

The short answer is No.

I think that it is important to state that the use of ketamine in [the area] was not a clinical trial. It was a standardized approach to the prescription of a “novel” treatment for TRD, with attempts to monitor response to identify whether or not there was benefit to any of the patients.

I hope that these responses to your questions will be of assistance.

Appendix B: Independent expert advice to the Commissioner — Associate Professor Miles

I am a duly qualified and registered medical practitioner practicing in the specialty of psychiatry.

My qualifications are:

MBChB (Otago) 1972;
Dip Psychiat (Auckland) 1981;
MD (Otago) 1982;
MRANZCP 1982;
FRANZCP 1987.

My work includes:

Rural psychiatry;
Clinical research in psychiatry and addiction;
Clinical Director of Awhina Research and Knowledge;
Deputy Chair of Northern X Ethics Committee.

I acknowledge that this combination of roles results in my experience being different to others who entirely practice as clinicians and that my involvement with the Ethics Committee for 6 years would have me more focussed on ethical issues in care and research than would be the standard for a practicing psychiatrist.

I am aware that this report was requested to assist the Commissioner in his consideration of:

- The appropriateness of services provided by Southern DHB to patients receiving ketamine on [Ward X], [the public hospital] in 2010 and 2011.
- The adequacy of information provided by Southern DHB to patients receiving ketamine on [Ward X], [the public hospital], including the informed consent process.
- The appropriateness of the services provided by [Dr A] to patients receiving ketamine on [Ward X], [the public hospital] in 2010 and 2011.
- The adequacy of information provided by [Dr A] to patients receiving ketamine on [Ward X], [the public hospital], including the informed consent process.

13 specific questions were posed as detailed in the body below.

The response is based upon:

1. Written material provided by the Commissioner which included:

- Complaint from [Mr B] (3 Dec 2010) plus HDC correspondence with him from that time.

- HDC communications with Southern DHB, including serial responses to issues raised.
 - HDC communications with [Dr A] and his serial responses to those inquiries.
 - Extracts from the patient notes of those patients who received ketamine that dealt with the information given, consents obtained, administration of treatment and observation of treatment.
 - Copies of papers cited by Southern DHB and [Dr A] that describe ketamine use in depression.
 - Successive drafts of information provided to patients, consent forms and observational protocols developed by [Dr A] and Southern DHB over the period in question.
 - National Health Board letter to HDC 19 December 2011.
 - Information from [Dr D], Southern DHB.
2. My awareness from my own reading and from conference attendance regarding the possible place of ketamine in treatment of depression (NOTE I have not performed a literature search or gained additional material outside that quoted above).
3. My awareness of the New Zealand standards and guidelines for
- Ethical approval of interventional study.¹
 - Use of unapproved medications.²
 - Innovative practice.³
 - Ethical considerations for case reports and case series.⁴
4. Consultation with a group of psychiatrist peers regarding the general issues of prescribing unapproved medicines BUT NOT specifically ketamine or the practices in the above material.

Question 1 With reference to relevant literature, standards and guidelines where appropriate; please clarify what constitutes the following, and the clinical context in which these terms are normally used:

- *a clinical trial/ clinical research;*
- *experimental prescribing/ treatment;*
- *“Off-label” or “novel” prescribing/ treatment.*

Clinical trials and clinical research

Though one might expect a clear definition of this and a clear application of guidelines accordingly it is my belief that across the clinical spectrum one would find a range of definitions and positions. These would extend from the view that clinical trials/research are never part of standard practice to the position that the knowledge we have about any single person’s response to an intervention, especially a drug, is unknown so any clinical intervention should be approached as if it were a “n = 1” clinical trial.

It is easy to see that carefully developed interventional study where the type or types of treatment are being assigned to patient groups in a controlled and randomised fashion are clinical research. The above mentioned guidelines are well known and fully used in these examples. There will be less clarity where the question being asked is answered by observational study, that is where the conditions under study are naturally occurring or the intervention is part of standard practice and occurs in a non-controlled fashion. “Innovative treatment” (which never gets raised in any of the material relating to this case) is a further confounder to those in search of a simple definition of clinical research (more will be said of this later).

In summary I believe that there would be a general view that clinical research spreads across intervention study, observational study and innovative practice.

Experimental prescribing and treatment.

In its widest sense experimental treatment would be seen as anything that occurred in clinical research.

It would not be infrequent however for there to be a narrower focus such that the “experimental” label was reserved for study that is in the early phase of investigation of the possible effect of an intervention. There is some scientific justification to think the treatment might have a desirable effect based on knowledge of anatomy and physiology but there is not yet evidence that it actually has the effect desired. This is easiest seen in what is called phase 1 study where a product is being tested for the first time in man to examine both the ability to produce the desired effect and to look for any unwanted effects. Such study is usually conducted with healthy human volunteers.

Equally the definition would apply to the phase 2 studies; these are those where the treatment in question is being used in people with the target health problem. They are designed to get early indication that the treatment does impact on the disorder in question and to see that it is safe in people with that health problem.

The next phase of clinical research then sets out to show that in a larger cohort of patients the treatment does in fact have a significant effect and does not cause undue harm (this sets out to show the number of people you would need to expose to the treatment to see the desired benefit [number needed to treat] as well as the number who experience adverse reactions [number to harm]). By this stage of the investigation of the treatment there would be a trend to see this less “experimental” but it would still be seen by all as clinical research.

“Off label” and “novel” prescribing/treatment.

The term “off label” arises from the fact that when a medicine is registered for use in a country it is for a specific set of indications (usually by disorder/diagnosis and sometimes for demographic details such as age). The manufacturer of the product is required to show this in the product information (“the label”). In most countries there is an acceptance that doctors may want or need to offer the treatment to people with indications that are outside that registered (i.e. “off label”).

The guidance around this use comes mostly from the Medicines Act and from the prescribing information related to that. In New Zealand Medsafe is the agency responsible for provision of that information. The Medsafe website gives guidance for doctors regarding their rights and responsibilities when prescribing unapproved medicines.

There will be a number of reasons why off label use is contemplated. A medicine may have a strong evidence base and may be in use in other countries regularly, but the manufacturer has not applied to have it registered for use in New Zealand. It may be that the medicine in question is registered in New Zealand but only for certain indications though the evidence base strongly supports the alternative indication. Sometimes research subsequent to the registering of the product establishes that the product registered for a particular use has a new effect.

The guidelines also address the times when the prescribing of an unapproved medicine where there is limited or no scientific evidence of the efficacy and safety. It is noted that in the guidelines the term “experimental” is introduced assumedly in relation to the amount of evidence regarding both efficacy and safety. Written informed consent must be obtained for such experimental “off label” use.

The term “novel” is not one I am used to seeing in this context; I would assume that it could be synonymous with “innovative practice” which refers to provision of an intervention that is untested, unproven or not in common use. The guidelines around such practice suggest peer discussion re the use of the innovative treatment should occur and Ethics Committee review be requested when there is doubt.

Question 2 “In your view, do the following categories accurately represent the situation that exists in New Zealand in relation to medical practitioners’ prescribing options? Please comment.

- *Prescribing of approved medicines for approved indications;*
- *Prescribing of approved medicines for unapproved indications (where there is a substantial evidence that the medication has accepted efficacy and safety in the treatment of the indication); and*
- *Prescribing of approved medicines for unapproved indications (where the evidence base for the safety and efficacy is not extensive and where use of the medicine for that indication is not common); and*
- *Use of experimental medicines.*

Much of this has been covered in the answers to question 1.

There could be a further bullet point; “*Prescribing of approved medicines for unapproved indications where there is no evidence for its use or the evidence would be against its use*”. It may be that this is seen to be subsumed under “experimental”.

I am not convinced that it is conceptually useful to put “use of experimental medicines” in this hierarchical list as there is not clarity of when use is experimental. If it were seen however as “*use in a clinical trial where Standing Committee on*

Therapeutic Trials (SCOTT) permission has been given for its use” then that would be a more logical flow.

The delineation regarding the range of available evidence is logical and there should be processes for review of use and consent processes for use that are dictated by that evidence range.

Question 3 What, in your understanding, are the approved clinical indications and uses for ketamine in New Zealand?

My understanding is that ketamine is only approved for use as an anaesthetic agent.

Question 4 In your view is the current evidence base for the use of ketamine for treatment-resistant depression adequate or sufficient to support off-label prescribing?

Question 5 In your view is there sufficient current evidence that ketamine is a safe and efficacious treatment for treatment resistant depression?

There is an encouraging but limited evidence base for the use of ketamine in treatment-resistant depression. Three small blinded trials demonstrated mood improvement following intra-venous use, but this was not sustained. These trials did not show safety concerns. It is reasonable to take the safety data from ketamine use in humans for anaesthetic purposes as likely to show a similar profile when used in depressed subjects. The numerous small number non-blinded studies also point to a rapid but non-sustained benefit. Presentations at international conferences over the past decade have referred to ketamine as a possible investigational product.

I see the evidence as justifying further controlled study to properly test the efficacy and safety of ketamine in treatment resistant depression but would not myself be persuaded that the current evidence would be sufficient to use it as a treatment now.

If one was contemplating use in an innovative treatment sense then I would have thought the evidence was at a level where one must consult peers before use and would be likely to also seek Ethics advice. Written informed consent would seem appropriate for such use.

From my previous knowledge of the agent and from the material presented to me the evidence for use of ketamine is for its intravenous use; I did not see evidence relating to intra-muscular use. I also note that in their letter to the Editor of [a journal in] 2011 [Dr A] et al state “several important technical questions about administration of ketamine have not yet been explored ... these include route of administration, dose-exposure relationship and exposure-dose response information...” I read this letter as evidence of the need for more study in this area. If this is indeed what was their opinion then one has to speculate on why the climate of practice in [the area] did not have this innovative treatment recognised for what it was and therefore treated accordingly.

Question 6 In your view is there any distinction between “routine” and “less common” off-label prescribing?

This matter is well covered in answers 1 and 2 above.

To summarise

There are a range of reasons for off-label prescribing that are predominantly defined by the scientific evidence for that product's use and the New Zealand product registration. The importance of considering the level of evidence is that evidence should define what a reasonable expectation regarding peer consultation and consent process should be.

The previously made comments about the definition of "innovative treatments" and its surprising absence from any of the discussion round the use of Ketamine in [the region] are also relevant here. I note reference to Southern DHB developing a policy in relation to prescription of unapproved medicine use. A draft was provided. I would hope that this policy would also address the issue of innovative treatment, what precautions should be taken, what peer review is expected and what ethical consideration needs to occur with different levels of innovative practice. The draft document only referred to Ethics opinion when it is part of a clinical trial.

I believe that the polarised position that appears to have been adopted in discussion of ketamine use between "research" and "off-label" (which has nothing to do with research) may be prevalent in the Southern DHB and could contribute to failure to find any middle ground regarding innovative practice.

Question 7 Please provide any comments you have in relation to [Dr A's] prescribing of ketamine for treatment resistant depression in patients on [Ward X] and his clinical trial relating to ketamine for cancer patients?

A. Clinical trial in cancer patients.

I note that this has been assessed and approved by an appropriately established New Zealand Health and Disability Research Ethics Committee. I must assume that committee has viewed the scientific justification, the trial design, the monitoring and risk and the informed consent process as I have seen their approval letter for the study. I did not see in that letter (though such may have been requested) that there was a need for SCOTT opinion. I raise this since to the best of my knowledge there is not evidence around the intra-muscular use of ketamine as proposed.

I also note that in that Ethics application there is a clear statement (see B5) that [Dr A] considers that "no part of the study would be considered standard treatment".

B. Use in [Ward X]

It is apparent that [Dr A's] evaluation of the available efficacy and safety data about the use of ketamine in treatment resistant depression is such that he considers the use is on a more secure base than I would have taken from the evidence provided. However that does not align to either the wording he uses in his Letter to the Editor of [a journal] or the above quoted statement in the Ethics application.

What is also important to note is the way in which the practice changed over time, from the first exposures being with limited written information and verbal consent to one which had fuller written informed consent and had an intervention protocol.

It is not evident in material provided to me the extent (if any) peer review occurred before the decision to embark on this innovative use of ketamine.

It is however clear that over the time period in question a number of [local] psychiatrists were aware of this prescribing. Some were quite closely involved in treatment reviews and decisions. Some were involved in the processes of provision of information and the gaining of consent. The material provided would suggest that the clinical leader of the service did not however have any awareness that this innovative treatment was being used.

In the material provided to me I could not find a justification for the intra-muscular use of ketamine. I note there is an article co-authored by [Dr A] that does raise this matter of equivalence of the IM versus IV doses. I note that all but one example of use in the material given us (and in all of the blinded studies) the use was IV.

From the records I had it would appear that all patients were given some level of explanation about the possible benefits and risks of the use of ketamine. The earliest use relied on verbal provision of information and verbal consent. I would have thought for such an innovative treatment written informed consent would have been prudent. I note that over time there was the development of an information sheet and a consent form obtaining written consent. The latest version of the information sheet finally made the innovative nature of the treatment clearer.

The material would suggest that care was taken in deciding the dose of ketamine to be used, in recording this in the clinical record, in careful provision of the treatment and in appropriate post injection monitoring for adverse reactions. I note that this record was sometimes created by medical students but most of those notes refer to the presence of a more senior doctor, often [Dr A]. There was longitudinal assessment of the target symptoms using established monitoring tools. I note also that there appears to be emerging over time a written protocol for the administration and monitoring; once again I would have thought such protocol development would have been prudent at the beginning of this innovative use.

Question 8 What is your understanding of the expected risks, side effects and benefits of the use of ketamine for treatment resistant depression?

The benefits of iv ketamine for treatment resistant depression is suggestive of a rapid but not sustained improvement in mood; as reported above I believe it is sufficient to suggest further trialling of the product but would not be sufficient to support regular use.

Apart from the safety data related to its use as an anaesthetic agent there is very limited information regarding its use in depression patients. It was apparent that monitoring for the short term effects likely to be distressing to these patients such as the dissociative experiences and possible perception changes occurred and any such reaction dealt with appropriately.

Question 9 In your view, based on the clinical reports available, was each of the 11 patients highlighted by this matter clinically indicated for ketamine use in treatment resistant depression, and competent to consent?

There is sufficient information to suspect that all eleven had treatment resistant depression though the notes I had would not allow that to be declared with certainty. A number appeared to also have co-morbid problems.

As to whether they were “clinically indicated” for the treatment such is not possible to decide as there are not clear grounds established for the use of this treatment in depression.

Again from the evidence I have while one cannot establish competence to consent with any clarity, there are not glaring reasons to suspect the patients were not competent. It is regularly accepted that people with severe depression per se are not excluded from being competent. The only possible exception was one subject where ECT was considered and a second opinion was obtained because of his borderline IQ. There was however no comment re any special provision for consent to ketamine use in that subject.

A consent issue that did not appear to be considered was that of “undue influence”. It is likely that most of these patients were desperate for treatment of their depression and therefore vulnerable to hearing the suggestion from their doctor [...] as their last hope. They could be inclined to agree without thinking through the facts such as the minimal evidence re efficacy and the fact this is an unapproved use. From the records it seems that some of the initial discussion regarding possible use was instigated by other members of the team. It did not appear, however, that this was a planned approach to diminish the power imbalance effect. It was also not evident that family or significant others were invited to be involved in the consideration of this innovative approach. I would again see such invitation as prudent.

Question 10 Please comment on the nature of the consent process that you and your peers would expect to eventuate in each of the above prescribing scenarios outlined in question 2.

- Prescribing of approved medicines for approved indications; verbal consent would be the norm, sometimes informational pamphlets might be given; most times would be with patient directly talking with doctor.
- Prescribing of approved medicines for unapproved indications (where there is a substantial evidence that the medication has accepted efficacy and safety in the treatment of the indication); verbal consent would again be the norm; explanation of the evidence base (if not already known by the patient) would be made and some explanation given as to why it is not approved in New Zealand.
- Prescribing of approved medicines for unapproved indications (where the evidence base for the safety and efficacy is not extensive and where use of the medicine for that indication is not common); the information given re both reason to suspect possible benefit and also the known safety data would be more carefully explained and frequently a written version would be prepared;

involvement of support in the decision would be suggested (friend or family) and time to consider would be mandatory; usually written consent* would be obtained and recorded. It is likely that external assessment of this use would have been obtained from either peer review or ethics committee or both, and this would also be explained to the patient.

- Use of experimental medicines; this would follow the usual full informed written consent to engage in a clinical trial which is probably much the same as for the previous example of innovative practice.

* It is felt by most that there needs to be a relationship process between the informer and the consentor that takes into account the person's understanding, perceptions and values. There is sometimes a situation with informed written consent where the interpersonal aspects of rapport establishment and verbal informing are seen as secondary or unnecessary, but this should never be the case. Therefore some believe more emphasis must be placed on the process and that written recording of a verbal consent process is fully acceptable.

Question 11 In your view does [Dr A's] prescribing of ketamine for treatment resistant depression fall in to any of the categories outlined in question 2? Please comment.

I would have thought that the use of ketamine would have fitted "Prescribing of approved medicines for unapproved indications (where the evidence base for the safety and efficacy is not extensive and where use of the medicine for that indication is not common)".

He appears to have acted as if he believed the use fitted "Prescribing of approved medicines for unapproved indications (where there is substantial evidence that the medication has accepted efficacy and safety in the treatment of the indication)".

Question 12 Based on the information provided please provide your over-view of the appropriateness of [Dr A's] prescribing of ketamine to treat patients with treatment resistant depression in [Ward X] [the public hospital] in 2010 and 2011.

1. Decision to use the treatment.

I would not have seen the use of ketamine in this situation as other than an innovative treatment and therefore there would be a different set of processes that would have been put in place:

- a. Properly conducted and well recorded discussion with peers and other relevant experts in the field and
- b. Depending on the collective advice submission of the innovative treatment to an Ethics Committee with
- c. Design of an appropriate use and monitoring protocol and
- d. Design of an appropriate information sheet and consent form.

2. Treatment administration

This appears to have been thoroughly and comprehensively conducted.

3. Adverse event monitoring

Again from the records we have this was attended to.

4. Outcome monitoring

Was conducted and appropriate screening tools were used.

Question 13 In answering any of the above questions do you believe that [Dr A] did not provide an appropriate standard of care; please indicate your view on the severity of his departure from that standard (and whether the provider's peers would view the conduct with mild, moderato or severe disapproval).

In my view the main point of departure from what I consider to be appropriate standard of care was in the consideration of the type of treatment, its novelty, and the need to apply regulations pertaining to innovative treatment. This departure I see as moderately severe departure from the New Zealand standards and guidelines as I read them. I believe this was an unfortunate departure since much of the rest of the care provision was, as far as the notes allow me to determine, at a level that would be seen as fully complying with expectations.

The second leg of this question does force speculation based on the limited information given me. The ongoing involvement of fellow [local] psychiatrists in the provision of this intervention and the monitoring of patients would suggest that his peers did not share my interpretation of the innovative nature.

It is also apparent looking at the email traffic with Southern DHB management that they also did not see the use of ketamine in this situation as innovative treatment requiring different consideration than would have been applied to off-label use with a high evidence base. I have already commented on the notification of the preparation by the DHB of a protocol for unapproved medicine use and its relevance to this case. There appears to be recognition that the presence of such a well defined policy may have made a difference.

One might speculate that the total system got trapped in to what was a very unhelpful process of trying to polarise this innovative use of ketamine in to "clinical research" versus "off-label clinical use", where one has an experimental connotation the other a compassionate treatment connotation. If there had been less drive to defend either position and an acceptance that there is a legitimate middle ground that is in fact a fertile ground for innovation in health care this matter might not have escalated as it has.

It may be useful for the Commissioner to encourage a New Zealand wide review of the way that regulations and guidelines re innovative practice and prescribing of medications for use outside of the approved use are translated by Health Authorities and medical practitioners such that innovative possibility is not stifled but that health care consumers can feel their rights and safety are well protected.

S W Miles
04.04.2012

References

1. Ethical Guidelines for Intervention Studies. NEAC. MOH Nov 2009.
2. MEDSAFE New Zealand website.
3. Operational standards for Ethics Committees. MOH 2006.
4. Ethical Guidelines for Observational Studies. NEAC. MOH December 2006".

Further expert advice

In your view, is there clear consensus among clinicians and academics in your field relating to the following issue:

At what point would the evidence base regarding the safety and efficacy of a treatment, transition from being considered “minimal” or “equivocal” to a point where it would be considered “sufficient” and strong enough to support, for example, off label prescribing of a particular medication for a specific clinical indication (such as off-label prescribing of ketamine for treatment-resistant depression).

I believe there would be a range of positions whose degree of “conservatism” would be a bit dictated by that person’s usual style; some people are a bit more prepared to explore new alternatives and take “calculated risks” than others. Some would not use a treatment unless there was a body of trial evidence that supported it having a desired effect and with good safety data. I suspect the majority would want evidence that the treatment has been used in humans safely and also have a modest degree of reported evidence that it does have a desired effect in the condition under question.

Is this solely related to the quantity and quality of RCTs completed and peer reviewed on an issue? What other information could support the evidence base?

While the more conservative position would require RCT evidence before they were prepared to use it many would be prepared to contemplate less. Safety data re exposure in man is essential. There would need to be either case reports attesting to benefit and or a strong theoretical/physiological argument for the product having the potential to produce benefit.

What do you consider would be the primary reason clinicians/academics opposing the use of ketamine for TRD would cite in order to argue that the evidence base is insufficient?

Most would be concerned at the lack of reports re efficacy. Another area of concern would be that the safety of use has been demonstrated as an anaesthetic agent and there could be other problems when used in “awake” situations.

Are you aware of ketamine having ever been prescribed for treatment resistant depression in either a hospital, community mental health, or clinical trial setting in any area of NZ other than at [the public hospital]?

I am not aware of this having been done but am aware of discussions amongst psychiatrists about the possibility.

Appendix C: Patients who received ketamine

<u>Patient</u>	<u>Verbal discussions/consent (per notes supplied)</u>	<u>Articles and/or written information given at first discussion</u>	<u>Date that written consent/information forms signed</u>	<u>Date of 1st injection (total per DHB records)</u>	<u>NHB/HDC contacts with consumer</u>
Patient 1	19 April 2010, Dr A explains use of IM ketamine. Verbal agreement to proceed noted.	Not noted in records	Nil	19 April 2010 (no medication chart entry for 19 April, but administration is recorded in clinical notes) (14)	Invited to meet NHB, but did not do so. Patient contacted by HDC. [Patient 1] said her recall was poor and she could not recall anything about the events at that time.
Patient 11 (dec)	19 May 2010. Dr A discusses possible use of ketamine. Info is to be given. Verbal consent noted. Plan includes “discuss possibility of giving IM ketamine @MDT”.	Noted in records on 19 May 2010 that Dr A will give Patient 11 info regarding ketamine.	Nil	19 May 2010. (2)	(deceased)
Patient 6	3 June 2010 Ward round with Dr A. (Intern Dr K took notes.) Notes that Dr E will discuss second opinion re treatment options (incl. ketamine). 4 June 2010, ketamine use explained by house surgeon including side effects. Future ECT explained. Verbal agreement noted.	Not noted in records	Nil	4 June 2010 (2).	Did not wish to be contacted by NHB. Contact with HDC, but consumer had difficulty recalling any issues at all.
Patient 9	17 June 2010, Intern Dr K records discussion re	Not noted in	Nil	18 June 2010	Did not wish to be contacted by

	<p>ketamine injection, effects, and process. Noted that patient willing to try this.</p> <p>Another entry 17 June 2010 states “[Dr A] has talked with [Patient 9] about plan...”</p> <p>18 June 2010 — [Dr A] notes “discussed IM ketamine...”</p>	records		(2)	<p>the NHB.</p> <p>Not able to be contacted by HDC.</p> <p>Consumer wrote a letter of support to NHB for ketamine use (received by NHB in 31 August 2011).</p>
Patient 7	<p>19 July 2010, [Dr A] explains on a ward round the benefits and side effects of ketamine.</p> <p>Verbal agreement noted.</p>	<p>Not noted in records.</p> <p>Patient told HDC she could not recall if written information was given.</p>	Nil	<p>19 July 2010</p> <p>(2)</p>	<p>Invited to meet the NHB but did not do so.</p> <p>HDC contact April 2012. Patient recalls speaking with Dr A. Very comfortable with process undertaken.</p>
Patient 10	<p>13 Sept 2010. Patient willing to try ketamine. Discussion with [Dr A] noted regarding effects and outcomes.</p> <p>After injection mood improves, “weight lifted”.</p>	<p>Noted on discharge form 17 Sep 2010, that “discussed IM ketamine as an option to lift mood — gave [patient 10] written information about this...”</p>	Nil	<p>13 Sept 2010</p> <p>(1)</p>	<p>Did not wish to be contacted by NHB.</p> <p>Did not respond to multiple HDC telephone messages or letter requesting contact.</p>
Patient 2	<p>15 September 2010 discussion with [Dr A] re ketamine risk, benefits, side effects. Verbally agrees. Article given to patient.</p> <p>Notes suggest the plan is to give Patient 2 more information about ketamine and procyclidine.</p>	<p>Noted in records (by med student) that an article was given.</p> <p>Consumer confirmed to HDC did receive article.</p>	<p>Readmission 22 Jan 2011.</p> <p>Signed 24 January 2011 (Sept 2010 version) Dr A</p> <p>Signed 19 August 2011 (April</p>	<p>16 Sept 2010</p> <p>(1)</p> <p>Then a further</p> <p>(8)</p>	<p>Invited to meet with NHB but did not do so.</p> <p>HDC contact Feb 2012. Patient cannot recall having any concerns at the time.</p>

			2011 version) [Dr A]		
Patient 8	<p>22 March 2011 — Dr G notes a plan to talk with Dr A about ketamine. RN also notes Dr E will discuss ketamine with Dr A.</p> <p>23 March 2011, discussion with patient regarding written material — aware that its use in depression is off label — before signing form.</p>	Noted in records that received.	<p>Signed 23 March 2011 (not an info form) not co-signed.</p> <p>Signed 1 April 2011 (Sept 2010 version) Dr G</p>	<p>24 March 2011</p> <p>(6)</p>	<p>Inpatient. Agreed to meet NHB.</p> <p>Unable to be contacted by HDC.</p>
Patient 4	29 April 2011, Dr A discusses ketamine treatment and options. Info sheet given and meeting with wife.	<p>Info/consent form.</p> <p>Patient confirmed to HDC that written material received.</p>	Signed 29 April 2011 (Sept 2010 version) Dr A.	<p>29 April 2011</p> <p>(1)</p>	<p>Agreed to meet NHB and did so.</p> <p>HDC phone contact March 2012. Patient expressed no concerns about the information or consent process.</p>
Patient 3	<p>16 May 2011, Dr A explains off-label use of ketamine. (Intern notes refer to this and the info sheet.)</p> <p>Discharge summary explains patient had spoken with Dr A who explained the off-label use and had given the info sheet.</p>	<p>Info/consent sheet</p> <p>Patient could not recall if he received written information or not.</p>	Signed 16 May 2011 (Sept 2010 version) Dr A.	<p>16 May 2011</p> <p>(1)</p>	<p>Invited to meet NHB. Did not do so.</p> <p>HDC contact Feb 2012. Patient had no concerns about the consent process.</p>
Patient 5	8 April 2011. Dr F and intern note that a discussion with the patient and family, Dr F and Dr A occurred prior	<p>Info/consent sheet</p> <p>Patient recalls receiving info</p>	Signed 7 April 2011 (Sept 2010 version) Dr	<p>8 April 2011</p> <p>(13 up to 23/12/11)</p>	<p>Agreed to meet NHB team and did so.</p> <p>HDC contact</p>

	to first administration. Consent form signed, discussion about future options including amantadine and procyclidine.	sheet citing articles	<p>A.</p> <p>6 May 2011 (Sept 2010 version) Dr A</p> <p>30 May 2011 (April 2011 version) Dr I</p> <p>19 July 2011 (April 2011 version) Dr A</p> <p>24 Nov 2011 (April 2011 version) Dr F</p>	Then treatment ongoing.	<p>May 2012. Found the information given to her very helpful. Considered it a “lifesaver treatment”.</p> <p>One of the patients who requested continued use despite DHB halting treatments after HDC investigation commenced.</p>
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