Psychiatric hospitalisation before and after commencing long-acting injectable antipsychotic medication: a mirror-image study

Marella Bedggood, Shirley Walton, Mayan Bedggood

ABSTRACT

AIMS: Treatment adherence is an important predictor of outcomes in schizophrenia, related disorders and bipolar disorder, and may be improved by the use of long acting injectable (LAI) antipsychotic medication. Past research on the efficacy of LAIs is mixed with randomised controlled trials showing similar benefits to oral medication, and naturalistic studies showing advantages to LAIs.

METHOD: Psychiatric hospital bed-nights and admissions were compared before and after commencement of an LAI, using a retrospective cohort study with a mirror-image design. Total bed-nights and hospital admissions for each patient were compared for the same time period before and after commencing the LAI. Subgroup analyses were also conducted.

RESULTS: Mean bed-nights decreased from 47.1 pre-LAI to 14.3 post-LAI, and median bed-nights from 24.5 to 0.0. Mean hospital admissions decreased from 1.7 pre-LAI to 0.7 post-LAI, and median admissions from 1.0 to 0.0.

CONCLUSION: In our cohort, LAI treatment was associated with a significant reduction in bed-nights and total admissions to psychiatric hospitals. The findings of the current study are consistent with the results of previous naturalistic studies of LAI treatment for patients with psychotic disorders and bipolar disorder.

Treatment adherence is an important predictor of relapse and psychiatric hospitalisations in schizophrenia, related psychotic disorders, and bipolar disorder.[1–3] Administration of antipsychotic medication in long-acting injectable (LAI) slow release formulations (also called depot antipsychotics) allows doses to be administered in the form of an intramuscular injection every two to four weeks instead of daily oral dosing, ensuring consistent medication delivery and more accurate monitoring of treatment adherence.

Results of randomised controlled trials (RCTs) comparing LAIs with oral antipsychotics have not shown any benefits of depot formulations over oral.[4,5] However, although RCTs are often considered the gold standard for assessing treatment efficacy, it has been suggested that they may be less appropriate for questions of best practice relating to antipsychotic treatment.[6–8] This is because RCTs are likely to select competent, consenting patients where adherence can be reasonably expected, and often involve the artificial scenario of frequent monitoring and reminders, potentially resulting in different therapy adherence than real-world settings as the trial itself can influence patient outcomes via the Hawthorne effect.[6,9] Therefore, results from RCTs alone may not be representative of real world differences in outcomes relating to antipsychotic treatment.[10,11] More pragmatic study designs can be valuable for assessing real-world population outcomes and their use complements findings from RCTs by adding to the generalisability of available evidence.[8,10] With this in mind, Kirson and colleagues[12] conducted a systematic review and meta-analysis of studies assessing efficacy of LAIs versus oral medications for relapse and hospitalisation, comparing results from RCTs versus observational studies. They found no evidence of a difference in efficacy when only RCTs were analysed, but found that there were significant advantages to LAIs when both prospective and retrospective observational studies were analysed.

Mirror-image studies are observational studies that compare periods before and after a certain condition is met, with a patient acting as their own control. The mirror image design is a well-recognised and useful methodology for psychiatric research and has been used by several international authors to examine psychiatric outcomes.[9,11,13–16] As each patient is compared to their previous experience and not with an aver-

age, this can be useful for research in disorders where individual illness courses vary widely.[17] Compared to RCTs, mirror-image studies allow for a more naturalistic representation of real-world antipsychotic treatment outcomes, especially regarding research questions where medication adherence is thought to be so important. In a systematic review of 25 mirror-image studies of 5,940 adults with schizophrenia or schizoaffective disorder, the overall risk of hospitalisation, rates of hospitalisation and time spent in hospital were compared before and after initiation of LAI treatment.[6] Strong evidence was found that LAI treatment was superior to oral treatment in preventing hospitalisations (risk ratio [RR]=0.43), as well as decreasing the number of days patients spent in hospital. Tiihonen and colleagues[7] studied the antipsychotic treatment of 29,823 patients with a diagnosis of schizophrenia using an alternate method of within-individuals analysis. They found that the risk of hospitalisation with LAI treatment was 22% lower than when patients were treated with the oral form of the same medication ($p<0.001$).

In order to obtain information from an Aotearoa New Zealand context, the authors conducted a retrospective observational study with a mirror-image design examining outcomes before and after commencing LAI antipsychotic treatment in our local community service. The number of nights spent admitted to a psychiatric hospital, or "bed-nights", were used as an outcome measure. As well as being correlated with relapse rates,[18] hospitalisation is an important end point in itself, given that psychiatric in-patient unit beds are a scarce resource that must be utilised with consideration of both the individual patient needs as well as the needs of the community as a whole. This is certainly true in the Aotearoa New Zealand context, where the number of psychiatric in-patient beds (32 per 100,000 population) is roughly half the average per capita for Organisation for Economic Cooperation and Development (OECD) member countries.[19,20]

Method

The Health and Disability Ethics Committee reviewed the study protocol (Reference 21/CEN/61) and approved the unconsented use of previously collected data for the study purposes.

Study population

All patients under the care of a district health board (DHB) general adult community mental health team, who were prescribed a second-generation LAI medication as of 31 December 2019. Only those prescribed a second-generation LAI were included in the initial cohort as the service keeps a centralised record of these patients. It was expected that the majority of included patients would have a diagnosis of schizophrenia, but we were also interested in the outcomes for patients with other psychotic disorders and bipolar disorder, given that patients with bipolar disorder often experience psychotic symptoms and antipsychotic medication is effectively utilised in the management of bipolar disorder.[21]

Inclusion criteria

Patients with a psychotic or bipolar disorder, prescribed a second-generation LAI of any kind as of end 2019, under the follow up of the identified community mental health service at end 2019, treated with an LAI for at least six months prior to end 2019.

Exclusion criteria

Patients with a personality disorder or unipolar depression with or without psychotic features as their only diagnosis, patients not living in the region during the period under consideration and therefore with hospitalisation and bed-night data not accessible. Only those patients with evidence of contact with mental health services prior to the start of the pre-LAI mirror period were included, to ensure that both periods of comparison covered a part of the patient's life after the onset of their illness. In the case where a patient's first contact with mental health services was later, the time period of the mirror was adjusted to this date.

Outcome measures

The primary outcome was bed-nights pre- and post-LAI. Bed-nights were defined as nights spent admitted to any of the DHB's psychiatric in-patient units. Total number of psychiatric hospitalisations (admissions) pre- and post-LAI commencement were also assessed as a secondary outcome.

Data collection

Electronic medical records were reviewed to retrieve the following information: LAI commencement date, LAI type, age, gender, ethnicity (by self-report), whether patients were subject to compulsory treatment under the Mental Health (Compulsory Assessment and Treatment) Act 1992 (MHA) at the time of LAI commencement (MHA status) and whether they were in-patient

or out-patient at time of commencement (in-patient status). Two mirror periods of equal length were determined for each patient—the period of time from LAI initiation until the end of the study period or until the LAI was ceased, whichever came first (the post-LAI period), and a matching length period of time immediately prior to starting the LAI (pre-LAI period). A DHB data analyst staff member provided the associated bed-nights and admissions data for each mirror period.

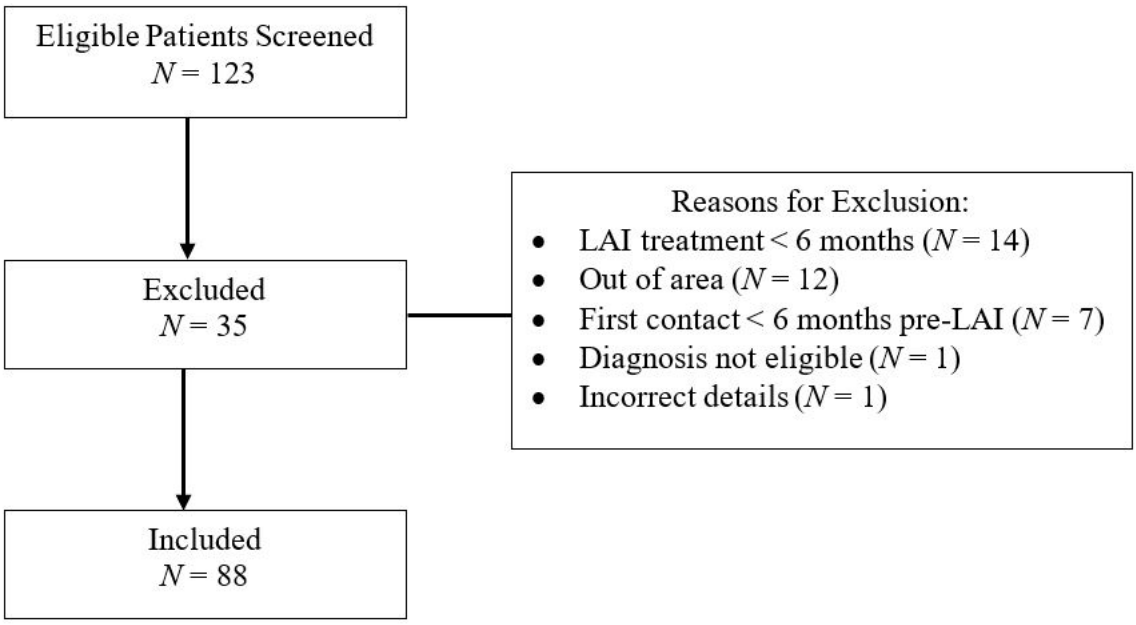
If a patient was prescribed more than one LAI but there was less than three months between the previous LAI and the current LAI, this was treated as one period of continuous treatment. When the date of LAI commencement fell during an admission, the remainder of bed-nights during that index admission were excluded, with the "mirror" starting from the date of discharge. For patients where their most recent episode of LAI treatment was not eligible for inclusion, if they had a prior period of LAI treatment then this was considered for inclusion instead whether they were prescribed a first- or second-generation LAI.

Statistical analyses were conducted using IBM SPSS Statistics (Version 28.0) and *p*-values of <0.05 were considered significant.

Results

After screening, 88 patients were included in the analysis (see Figure 1). Baseline patient characteristics are summarised in Table 1.

Figure 1: Patient screening.



Preliminary analysis

The assumption of normality was violated as indicated by significant Shapiro–Wilk tests for both the bed-nights (W=0.75; $p<0.001$) and admissions data (W=0.96; $p=0.006$); therefore, the Wilcoxon signed-rank test was used.

Primary analysis

Bed-nights pre- and post-LAI were compared using the Wilcoxon signed-rank test. Results indicated that there was a significant reduction in bed-nights post-LAI (*Mdn*=0.0; *M*=14.3; *SD*=33.0) compared to pre-LAI (*Mdn*=24.5; *M*=47.1; *SD*=64.9), z=-5.29; $p<0.001$, with a medium effect size of $r=0.40$ (see Figure 2).

Secondary analysis

Admissions pre- and post-LAI were compared using the Wilcoxon signed-rank test. Results indicated that there was a significant reduction in admissions post-LAI (*Mdn*=0.0; *M*=0.7; *SD*=1.5) compared to pre-LAI (*Mdn*=1.0; *M*=1.7; *SD*=1.4), z=-4.93; $p<0.001$, with a medium effect size of $r=0.37$ (see Figure 3).

In the pre-LAI period, only 17 out of 88 patients (19.3%) had no in-patient admissions at all, whereas this increased to 65 patients (73.9%) in the post-LAI period (see Figure 4).

Subgroup analyses

Subgroup analyses were conducted with descriptive statistics for each subgroup summarised in Table 2.

Table 1: Baseline characteristics.

Characteristics	Totals (%)
Age bands (years)	
18–29	10 (11.4)
30–39	20 (22.7)
40–49	21 (23.9)
50–59	20 (22.7)
60+	17 (19.3)
Gender	
Female	27 (30.7)
Male	61 (69.3)
Ethnicity	
Non-Māori	80 (90.9)
Māori	8 (9.1)
Diagnosis	
Schizophrenia	58 (65.9)
Schizoaffective disorder	15 (17.1)
Bipolar disorder	10 (11.4)
Psychotic disorder not otherwise specified	3 (3.4)
Substance-induced psychotic disorder	1 (1.1)
Delusional disorder	1 (1.1)
Type of LAI medication	
Olanzapine	31 (35.2)
Paliperidone	22 (25.0)
Risperidone	19 (21.6)
Flupenthixol	2 (2.3)
Mixed	14 (15.9)
Length of mirror period (days)	
Mean	1,085.0
Median	839.0
Minimum	184
Maximum	3,703

Figure 2: Average bed-nights pre- and post-LAI.

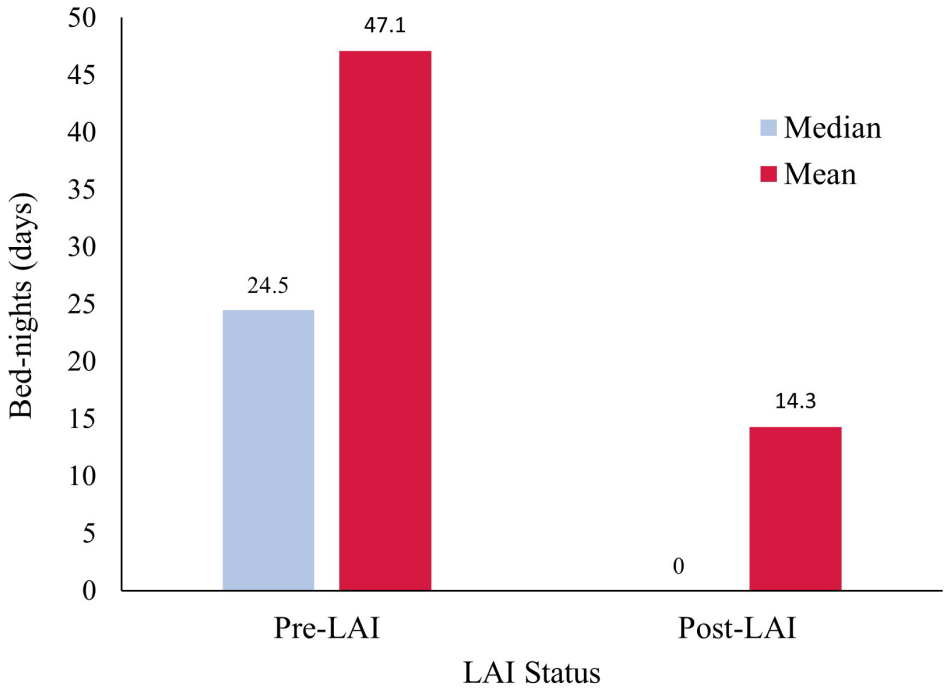


Figure 3: Average admissions pre- and post-LAI.

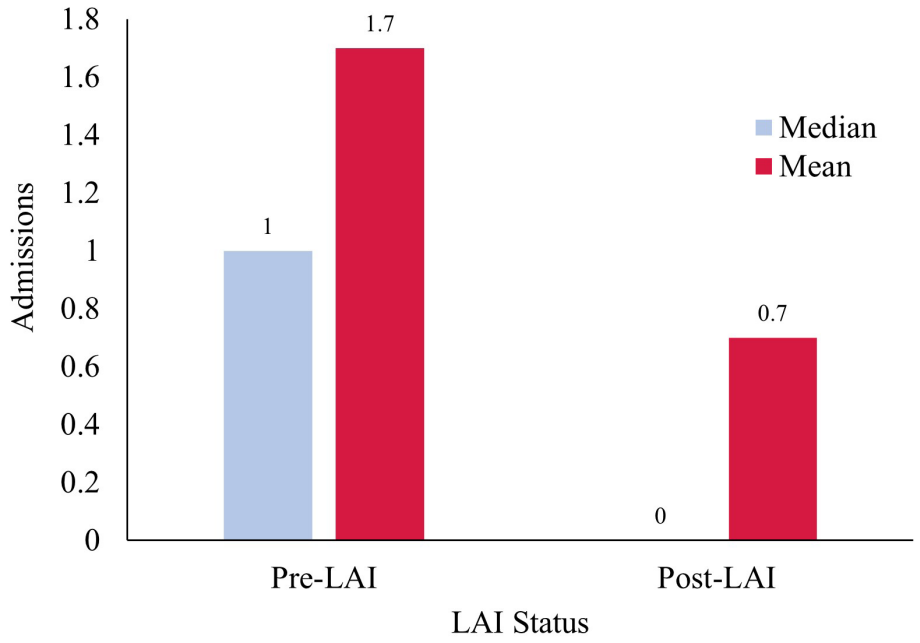


Figure 4: Change in proportion of patients with no admissions.

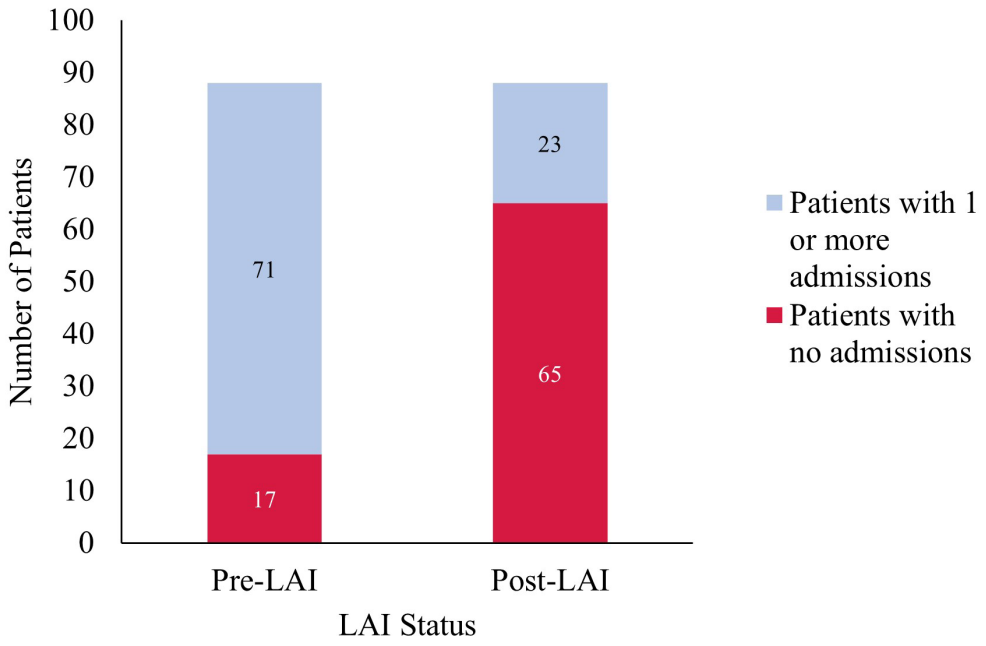


Table 2: Subgroup analyses for ethnicity, MHA status and in-patient status.

	Bed-nights				**Admissions**			
Sub-group	**Pre-LAI**		**Post-LAI**		**Pre-LAI**		**Post-LAI**	
	Mdn	**M**	**Mdn**	**M**	**Mdn**	**M**	**Mdn**	**M**
Ethnicity								
Non-Māori	22.5	48.5	0.0	14.7	1.0	1.8	0.0	0.7
Māori	32.5	33.0	0.0	11.1	1.5	1.4	0.0	0.8
MHA Status								
MHA	33.0	57.1	0.0	16.9	2.0	2.1	0.0	0.8
No MHA	0.0	15.1	0.0	6.3	0.0	0.6	0.0	0.5
In-patient status								
In-patient	33.0	56.5	0.0	17.7	2.0	2.2	0.0	0.9
Out-patient	0.0	27.9	0.0	7.4	0.0	0.8	0.0	0.4

Ethnicity

A Mann–Whitney U test indicated that there was no significant difference between Māori (*Mdn*=18.5; *M*=21.9) and non-Māori (*Mdn*=13.5; *M*=33.8) patients in terms of the change in bed-nights after commencing an LAI (p=0.81). Another Mann–Whitney U test also found no significant difference in change in admissions between Māori (*Mdn*=1.0; *M*=0.6) and non-Māori patients (*Mdn*=1.0; *M*=1.1), with p=0.56.

MHA status

A Mann–Whitney U test indicated a significant difference between change in bed-nights for the MHA (*Mdn*=22.5; *M*=40.0) and no MHA groups (*Mdn*=0.0; *M*=8.9), with $p<0.001$. A significant difference was also shown for change in admissions between the MHA (*Mdn*=1.0; *M*=1.3) and no MHA groups (*Mdn*=0.0; *M*=0.1), with $p<0.001$.

In-patient status

A Mann–Whitney U test was conducted to compare the change in bed-nights based on in-patient status and indicated a significant difference between the in-patient (*Mdn*=22.5; *M*=39.2) and out-patient groups (*Mdn*=0.0; *M*=20.5), with p=0.003. Lastly, a Mann–Whitney U test indicated a significant difference for change in admissions between the in-patient (*Mdn*=1.0; *M*=1.3) and out-patient groups (*Mdn*=0.0; *M*=0.4), with $p<0.001$.

Discussion

For this cohort, the median nights spent in hospital after starting an LAI dropped from 24.5 nights pre-LAI to zero nights post-LAI. Additionally, the proportion of patients with no admissions at all, which was only 19.3% in the pre-LAI period, more than tripled to 73.9% in the post-LAI period. This degree of change was statistically significant and would likely also be of clinical significance.

The current study provides information on outcomes of LAI use from an Aotearoa New Zealand context and includes data from Māori patients, which at time of writing has not previously been published. It is known that Māori have higher rates of mental illness,[22] are admitted to psychiatric in-patient units at a higher rate than non-Māori,[23] and are more likely to be admitted due to schizophrenia.[24] This is of relevance to the current study as patients prescribed LAIs commonly have a diagnosis of schizophrenia, and are often subject to involuntary treatment under the MHA.[25] Given there is every reason to expect Māori to be prescribed LAIs at least at the same rate as non-Māori, ensuring equitable outcomes is imperative and in accordance with Article 3 of Te Tiriti o Waitangi.[26]

In our cohort, we found similar benefits for Māori and non-Māori groups in terms of change in bed-nights or admissions. However, there was only data available from eight Māori patients. A power analysis indicated that the effect size would have needed to be approximately 0.9 in order for a difference to be detected between Māori and non-Māori with the existing sample sizes. Although our cohort included a similar proportion of Māori (9%) to that of the DHB catchment area (10%),[27] Māori comprise 16.5% of the population in Aotearoa New Zealand and so were under-represented in this study.[28] We also considered looking at Pasifika patients as a separate group; however, there were only two Pasifika patients in this cohort (similar to the catchment area population).[29]

A further subgroup analysis was conducted for the effect of MHA status at the time of LAI commencement. The reduction in both bed-nights and admissions was greater for those under the MHA at the time of LAI commencement, compared to those who accepted the LAI voluntarily while not subject to the MHA. This may be because the benefits of LAIs are more pronounced in those patients that are not being treated in a voluntary capacity and are, therefore, likely to be less willing to take oral medication.

Lastly, a similarly significant result was found for the subgroup analysis comparing differences based on in-patient status. The reduction in both bed-nights and admissions was greater for those who were in-patients at the time of LAI commencement, compared to those who were out-patients. This may be because patients commenced as an out-patient would generally be more well, possibly with greater insight into the need for treatment, and more likely to be accepting of treatment, whether it be oral medication or an injection.

We believe that a strength of the methodology of this study is that no conditions were placed on treatment prior to the LAI. While many previous studies have sought to compare treatment with oral versus injectable antipsychotics, including patients with evidence of treatment with oral antipsychotics prior to LAI use has the potential to introduce selection bias. This is because any attempt to include those consistently adhering to an oral medication regimen encounters the same issues as RCTs, with unrealistically organised and adherent populations being included that do not

represent the populations of interest. It could be argued that in order to be more generalisable, study inclusion should place no conditions on the treatment prior to starting the LAI. This approach was taken by Taylor and colleagues[13] in a mirror-image study of paliperidone LAI with a naturalistic cohort of patients with diagnoses including schizophrenia, other psychotic disorders, or bipolar disorder. They found that paliperidone LAI initiation was associated with a decrease in both number of hospitalisations as well as total days spent in hospital.

There are, however, some important limitations to the mirror-image methodology that apply to the current study.[6] In contrast to a more formal RCT, mirror-image studies cannot rule out potential biases such as the unknown influence of both patients and prescribers being aware of the type of treatment, or time related changes in hospital admissions such as due to population growth with increasing bed pressure, availability of alternatives to hospital care (such as respite facilities), or change in clinical practices over time.[14] It is possible that these factors could introduce a systematic bias wherein later periods of time would have a tendency towards having shorter admissions, which was not controlled for in this study. The study is thus limited by the absence of a contemporaneous comparator. However, it is worth noting that a 2018 Health and Disability Commissioner Annual Report indicated that the average length of in-patient admissions in the four years prior to the end of the study period had been stable.[30]

A further limitation of the study is that only one region was analysed, which could have resulted in admissions not being counted if patients were living out of area when an admission occurred, as well as limited the generalisability. This study design could be expanded to other community teams and therefore be more generalisability to Aotearoa New Zealand as a whole.

In conclusion, the current study contributes data from the Aotearoa New Zealand context regarding the real-world outcomes for patients started on LAI antipsychotics. In our cohort, patients spent significantly less time in a psychiatric hospital after starting LAI medication as measured by both bednights and total admissions. This effect was greater for those who were commenced on LAIs while under the MHA or as in-patients. The same benefits were found for Māori and non-Māori patients, but numbers of Māori were small in this cohort. We hope that future research could investigate larger populations in other catchment areas with a higher number of Māori and Pasifika patients, and that it could be further expanded to take into account issues such as reasons for hospitalisation and access to treatment to further develop understanding of any differences in outcomes.

COMPETING INTERESTS
The authors declare no conflicts.
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