

**A retrospective observational study of the effectiveness of  
long acting antipsychotic injectable on hospital  
admissions**

by

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**SUBMITTED TO THE UNIVERSITY OF CAPE TOWN**

**In partial fulfilment of the requirements for the degree**

**Master of Medicine (MMed) in Psychiatry**

**Faculty of Health Sciences**

**UNIVERSITY OF CAPE TOWN**

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## **Declaration**

I, Bhaskaran Nathamaniar Charles, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work, nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. Furthermore, this work has not been reported or published prior to registration for this degree.

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## Abstract

**Background:** The impact on hospitalisations/ relapse rates of utilising long-acting antipsychotic injectable (LAIs) in a South African population suffering from chronic psychotic spectrum mental illness is poorly researched.

**Aim:** To compare the duration and number of hospitalisation episodes 12 and 24 months before and after the initiation of a LAI.

**Setting:** Valkenberg Hospital's adult acute inpatient psychiatry services.

**Method:** This was a retrospective naturalistic observational mirror-image study. Hospitalisation was utilised as a proxy for relapse.

**Results:** Sixty-one patients were identified for the study. A comparison of the 12 months before LAI initiation to the 12 months following LAI initiation showed a reduction in the number of admissions of 44% (55 to 31), and a reduction in the number of inpatient days of 23% (1892 to 1464). There was a statistically significant reduction in the median number of hospital admissions ( $p = 0.005$ ) and median inpatient days ( $p = 0.040$ ).

Comparing the 24 months before to the 24 months following LAI initiation, there was a reduction in the number of admissions of 30% (91 to 64) and inpatient days of 4% (3477 to 3355). There was a statistically significant reduction in the median number of hospital admissions ( $p = 0.014$ ) and a non-statistically significant reduction in median days ( $p = 0.428$ ).

**Conclusion:** The prescription of a LAI reduced the duration and number of hospital admissions over a 12-month period. After 24 months, there were fewer admissions but no significant reduction in the number of inpatient days. This study supports findings of international mirror-image studies.

## **Acknowledgements**

I would like to thank the following people:

- Ms D Constant for statistical analysis support
- Mr W Massembouri for statistical analysis support
- Dr N Horn in his capacity as supervisor
- Dr P Williams-Ashman in his capacity as co-supervisor

## Abbreviations

|        |  |
|--------|--|
| ACT    | Assertive Community Treatment team                                 |
| CI     | Confidence interval  |
| FGA    | First-generation antipsychotic                                     |
| HFU    | High-frequency user  |
| LAI    | Long-acting antipsychotic injectable                               |
| LFU    | Low-frequency user   |
| NNT    | Number needed to treat   |
| OAP    | Oral antipsychotic   |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analysis |
| RCT    | Randomised controlled trial  |
| RR     | Risk ratio   |
| SGA    | Second-generation antipsychotic                                    |

## Chapter 1: Introduction and literature review

### Background:

Psychotic disorders like schizophrenia and schizoaffective disorder are severe mental illnesses that are chronic, characterised by multiple relapses throughout the lifespan of a patient. The relapses often lead to repeated hospitalisations with an associated increase in burden of cost, worsening symptoms, impaired functioning, cognitive deterioration and reduced quality of life (Rabinowitz et al., 2007; Andlin-Sobocki and Rossler, 2005; Olivares et al., 2013). There is no curative management, and symptom relief is the one of the major goals of treatment. Antipsychotic medication is often required for long periods to minimise the distress associated with symptoms and reduce the likelihood of relapse. The lifetime prevalence of all psychotic disorders is 3.06% (Perala et al., 2007) with roughly 1% of individuals suffering from schizophrenia (Regier et al., 1993). In 2004, the World Health Organization estimated that over 26.3 million people worldwide and 2.1 million people in Africa suffered from schizophrenia (World Health Organization, 2004).

### Prevention of relapse:

Relapse prevention is identified as a key therapeutic aim in the treatment of psychotic illnesses. There is still no exact definition of relapse which is accepted internationally. Within research studies, hospitalisation is the commonest used proxy for relapse, followed by a change in clinical scales (Positive and Negative Syndrome Scale [PANNS] score, Clinical Global Impression [CGI] scale), exacerbation or re-emergence of symptoms, deliberate self-harm, change of medication, and social functioning (Olivares et al., 2013). Continuous antipsychotic medication has been shown to improve clinical outcomes in people with schizophrenia and reduce economic burden secondary to reduced relapse and hospitalization rates, shorter duration of hospitalisation, and fewer emergency room visits (Olivares et al., 2013; Stevens et al., 2015). In 2003, Leucht et al. found the risk of relapse is 2–6 times higher without antipsychotic medication in a systemic review of randomised controlled trials examining relapse rates in patients with schizophrenia (Leucht et al., 2003). Patients on medication at one year were shown by Hogarty and Ulrich in 1998 to have a relapse rate of 40%, while those who discontinue their treatment have



a one-year relapse rate of 65% and a two-year rate of >80% (Hogarty and Ulrich, 1998). Weiden et al. examined the relationship between adherence and rehospitalisation and reported that poor adherence to antipsychotic medication is a significant factor associated with relapse and rehospitalisation (Weiden et al., 2004). Olivares et al. reviewed 150 publications and studies that discussed relapse in patients with schizophrenia and found that the 95 most frequently reported factor was adherence problems (21/95) followed by stress/depression (11/95) and substance abuse (9/95) (Olivares et al., 2013). Non-adherence is associated with significant poorer functional outcomes, including use of emergency psychiatric services, arrests, violence, victimisation, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems (Ascher-Svanum et al., 2006).

In a South African sample, 217 patients with schizophrenia ~~were monitored in~~ an ~~who attended at least once in an~~ outpatient setting over ten years ~~were assessed~~. Two-thirds of the study population with schizophrenia did not adhere to their treatment and of those who were not adherent, 80.4% experienced a relapse (Kazadi et al., 2008).

#### Rationale for LAIs:

Continuous medication for chronic psychotic conditions which reduces relapses can be prescribed and administered either as oral formulations or as a depot injectable. Oral formulations are administered as tablets or capsules and are dosed once or twice daily. A depot injectable is administered as an intramuscular injection and dosed typically two-weekly or four-weekly. There are several recommendations for when to initiate a LAI. The National Institute for Health and Clinical Excellence (NICE) guidelines stipulate considering a LAI according to patient preference after an acute episode and when avoiding covert non-adherence (either intentional or unintentional) is a clinical priority (National Institute for Health and Care Excellence, 2014). The American Psychiatric Association stipulates that patients with recurrent relapses related to non-adherence are candidates for a LAI or those who prefer a LAI (American Psychiatric Association, 2004). The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders state that long-acting intramuscular preparations should be considered for maintenance on the basis of patient preference or convenience, or to manage non-adherence (Emsley and

Seedat, 2013). In clinical practice, patients and clinicians are sometimes reluctant to use LAIs because of stigma, needle pain, time constraints, side-effect concerns, and cost (Waddell and Taylor, 2009).

Non-adherence to antipsychotic medication can limit their efficacy. Patient non-adherence with oral formulations of antipsychotics is very common and is associated with a much higher chance of relapse compared to adherence with oral formulations of antipsychotics. (Byerly et al., 2007). The discontinuation rate for oral antipsychotics in schizophrenia ranges from 26% to 44%, and as many as 66% of patients are at least partially non-adherent (Kaplan et al., 2013). LAI therapy is a useful alternative treatment option that has comparable effectiveness and tolerability to oral antipsychotics (OAPs) while not requiring daily adherence (Stevens et al., 2015; Brnabic et al., 2011). Viala et al. studied 25 patients with a diagnosis of schizophrenia hospitalised for the first time in France. They were treated with LAI risperidone and reintegration methods and showed both a clinical improvement after 18 months, and very few relapses and re-hospitalisations (Viala et al., 2012). Their effectiveness is considered to be better than OAP via improved adherence, not via intrinsically better efficacy (Kishimoto et al., 2014). The prescribing of a LAI as the sole intervention for non-adherence has not been consistent as it was not shown to be adequate without effective intervention to modify negative attitudes (Kaplan et al., 2013).

Botha et al. analysed in a South African psychiatric population the variables that differentiated a high-frequency user (HFU) and low-frequency user (LFU) of hospital services. Only adult patients with a diagnosis of schizophrenia or schizoaffective disorder were included. High-frequency users were defined as those with multiple admissions to one of the three major tertiary psychiatry hospitals in the Western Cape. They found that being on a LAI was a significant association in the LFU group. However, none of the LFUs were treatment-resistant, which means the HFUs' relapse and readmission rates could be attributed to illness severity rather than treatment efficacy with a LAI. Also of note, both groups had high rates of poor compliance (Botha et al., 2010).

LAI also provide clinicians and caregivers with the opportunity to easily detect non-adherence as the two-weekly or four-weekly dosing is easier to monitor than the oral daily or twice-daily dosing. The injectable also has to be administered by a health professional who can inform carers and mental health care professionals if the patient has missed an injection date. This may allow for an early intervention regarding adherence challenges before a relapse. This ensured contact with a mental health professional also allows an opportunity for psycho-education. An additional advantage of LAIs is that they have a longer pharmacological half-life than OAPs. This allows a longer period for intervention than OAPs for missed doses before plasma levels drop below critical thresholds, where the risk for relapse, hospitalisation and suicide may be increased (Stevens et al., 2015).

#### Evidence base for LAIs:

The evidence for the effectiveness of LAI treatment over OAP treatment regarding relapse rates is mixed when comparing randomised controlled trials (RCTs) to mirror-image studies.

In 2009, Haddard et al. published a systematic review comparing first-generation antipsychotic (FGA) LAIs with OAPs in patients with schizophrenia. They reviewed randomised controlled trials, observational studies and mirror-image studies. The meta-analysis of RCTs showed no difference in relapse between OAPs and FGA-LAIs in 848 patients. Out of four prospective observational studies, two studies reported lower discontinuation rates for FGA-LAIs compared with oral medication, and two found that outcome was either no different or better with OAPs. Eleven mirror-image studies consistently showed reduced inpatient days and admissions following a switch from OAP therapy to FGA-LAIs. (Haddad et al., 2009)

In 2013, Kishimoto et al. published the largest known meta-analysis of mirror-image studies that compared the period before and after initiation of LAI treatment in adults with schizophrenia and schizoaffective disorders who had been treated previously with OAP treatment. The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and included studies up until 2012. Twenty-five mirror-image studies from 28 countries were included. They included 5940 patients that were followed up for at least  $\geq 12$  months ( $\geq 6$  months each on OAP and LAI treatment) and included

hospitalisation or relapse-related data. The reporting of relapse-related outcomes differed widely in mirror-image studies. Some reported hospitalisations for each patient before and after the initiation of the LAI. Some included patients that had only one hospitalisation prior to the LAI and stopped the follow-up when the patient had one relapse. Some reported hospitalisations as totals before and after the initiation of the LAI. Risk of hospitalisation was computed as the number of patients hospitalised divided by the number of patients at risk. The risk ratio was then determined by the ratio of risks for LAI versus OAP. Rate of hospitalisations was calculated by the number of hospitalisations divided by the person-years at risk. The rate ratio was then given by the ratio of rates for LAI versus OAP.

The mean duration of the study's follow-up in the included meta-analysis was 20.9 months. In all the studies, patients were switched from OAP to LAI and not the other way around. The choice of OAP included in the OAP phase was not controlled except in one study, and often it was not recorded. The type of LAI used in the LAI phase was documented: ten studies used risperidone (40%); eight studies used fluphenazine (32%); two studies used mixed or any FGA (8%); one study used clopenthixol, perphenazine and flupenthixol (4%); and one study used risperidone or FGA (4%).

The results showed LAIs were significantly superior to OAPs in preventing hospitalisations, ~~strong superiority of LAIs compared to OAP treatment~~. Specifically, LAIs showed strong superiority over OAPs in preventing hospitalisation (studies = 16; n = 4066; RR = 0.43;  $p < 0.001$ ). Fourteen of the 16 studies specifically showed statistically significant superiority. LAIs also showed superiority in decreasing the number of hospitalisations (studies = 15; n = 6342 person-years; RR=0.38; 95% CI: 0.28–0.51;  $p < 0.001$ ). This strong advantage was also observed for secondary outcomes: LAIs were significantly superior in reducing the days the patient was hospitalised (studies = 7; Hedges  $g = 0.77$ ; 95% CI: 0.22–1.33;  $p = 0.0063$ ). In a subgroup analysis of clinically relevant subpopulations and treatment groups, LAIs continued to show superiority over OAPs when looking at FGA-LAIs versus second-generation antipsychotics (SGA) LAIs; publication year of study; study sample size; region; pharmaceutical sponsorship; and data acquisition design in the LAI phase (Kishimoto et al., 2013).

In 2014, Kishimoto et al. published a meta-analysis of 21 RCTs following the PRISMA guidelines where LAIs were compared to OAPs in reducing relapses. The meta-analysis included 21 RCTs with 5176 patients. Most of the patients had a diagnosis of schizophrenia and schizoaffective disorder, though other diagnoses were included if the majority in the study had a diagnosis of schizophrenia or schizoaffective disorder. Patients were adults (17 years or older). The studies had to be for a minimum of 24 weeks: 12 weeks on an OAP, and 12 weeks on a LAI. They had to include information on relapse or hospitalisations. The primary outcome in the meta-analysis was study-defined relapse at the longest time point or, if no definition was available, predominantly psychiatric hospitalisations were used or, if these were not available, study-defined symptomatic worsening. The pooled relative risk with a confidence interval was computed using the random-effects model. The primary analysis used relapse rates based on survival scales and then was later repeated using the relapse rates of the initial sample size.

Thirteen of the 21 studies in the meta-analysis only included outpatients. Seven studies were open; five were rater-masked, and nine had a double-blind, double-dummy design. Each LAI was compared to OAPs individually, and LAIs were pooled and compared to OAPs. Out of the 21 studies included, ten studies involved a switch from an OAP to a FGA-LAI, and 11 studies to a SGA-LAI. Eight studies used fluphenazine; one study haloperidol; one study zuclopenthixol, and 11 studies risperidone. The median number of patients per study was 105. The mean duration of the studies was 66.4 weeks (range 24–130 weeks).

Overall, the authors showed that the pooled LAIs did not reduce relapse compared to OAPs in patients with schizophrenia and schizoaffective disorder. There was also no difference between the pooled LAIs and OAPs when considering secondary outcomes: relapse at 3, 6, 12, 18, and 24 months, all-cause discontinuation, discontinuation due to adverse events, drug inefficacy (i.e., relapse and discontinuation due to inefficacy), hospitalisation, and non-adherence. LAIs were not shown to be superior to OAP in subgroup analysis examining medication (FGA versus SGA); publication year; treatment concealment; inpatient versus outpatient status; study duration; medication allocation; and only outpatient studies lasting  $\geq 1$  year.

Regarding relapse rates, only fluphenazine showed significant superiority over OAPs (studies = 8, n = 826, RR = 0.79, 95% CI: 0.65–0.96,  $p = 0.02$ , NNT = 13). The other LAIs were not significantly superior to OAPs and, when pooled together, there was no overall significant superiority (studies = 21, n = 4950, RR = 0.93, 95% CI: 0.80–1.08,  $p = 0.35$ ).

The relapse rates at specific points (3, 6, 12, 18, and 24 months) for the pooled LAIs were similar to the OAPs. However, a single study with 105 patients that used fluphenazine showed trend-level superiority at 18 months (RR = 0.66, 95% CI: 0.44–0.99;  $p = 0.05$ ) and significant superiority at 24 months (RR = 0.56, 95% CI: 0.38–0.80,  $p = 0.002$ ). Two studies with 1445 patients showed trend level inferiority at 6 months (RR = 1.27, 95% CI: 0.97–1.66;  $p = 0.09$ ).

Pooled LAIs showed trend-level superiority in preventing hospitalisation over OAPs (studies = 10, RR = 0.89; 95% CI: 0.78–1.02;  $p = 0.09$ ). FGA-LAIs compared to SGA-LAIs were significantly superior to OAPs in preventing relapse (studies = 10; n = 897; RR = 0.82; 95% CI: 0.69–0.97;  $p = 0.02$ ). However, the results may have been affected by publication bias as they included only fluphenazine studies published prior to 1991 (Kishimoto et al., 2014).

The conflicting evidence between the meta-analysis of RCTs and mirror-image studies may be explained as follows: the participants in RCTs might be over-represented by patients with better engagement with health care providers, better adherence to the treatment, lower illness severity (particularly with increasing stringency of consent processes), and better cognitive capabilities to understand complex issues. In addition, participation in a controlled trial alters the natural ecology of treatment delivery and experience, including receiving more, and different types, of attention. More frequent monitoring during a trial also enables psychiatrists to change dosages according to the symptoms and provide supportive counselling (Kishimoto et al., 2014; Kishimoto et al., 2013).

~~Large database mining studies have also been conducted to test for the effect of initiating a LAI. Offord et al. compared hospitalisations and incidence of relapses by examining large commercial and Medicare health database claims in the United States. Schizophrenia related admissions were compared 12 months before initiation of a LAI or an OAP to 12 months after. A total of 2610 patients were identified and~~

~~they found a significantly greater reduction in the mean number of schizophrenia-related hospitalisations and associated length of stay when using a LAI (Offord et al., 2013).~~

~~A study by Bera et al. identified 5694 patients with schizophrenia on the Medicaid insured database in the United States. Study requirements were six months of treatment of OAP before initiation of LAI. After a mean follow up duration of 25.7 months, the study showed a significant decline in the number of schizophrenia-related hospitalisations as well as schizophrenia related length of hospital stay (Bera et al., 2013).~~

Regarding cohort studies, in 2011, Tiihonen et al. examined a nationwide cohort study in Finland that enrolled 2588 patients hospitalised for the first time with a diagnosis of schizophrenia. The risk of rehospitalisation for patients receiving depot medications was about one-third of that for patients receiving oral medications of the same compound (Tiihonen et al., 2011).

Considering case-control studies, Barrio et al. assessed the effectiveness of LAI risperidone versus OAPs in the treatment of recent-onset schizophrenia in Spain. After two years, there was a non-significant improvement in hospital readmissions and relapse rates with risperidone LAI over OAP (Barrio et al., 2013).

In South Africa, Emsley et al. undertook extensive local research on the treatment of schizophrenia and related psychotic illness with OAP and LAI treatment. They compared the relapse results of an open-label study in which 50 patients were treated with LAI risperidone with the relapse results of a randomised controlled trial in which 47 patients used oral risperidone and haloperidol. The patients were from Stikland Hospital, a tertiary psychiatry hospital in the Western Cape, and included only those patients with schizophrenia, schizoaffective disorder and schizophreniform disorder. Their findings showed a significantly lower relapse rate in patients on LAI versus OAP (Emsley et al., 2008).

Large analysis of pharmaceutical databases have also been conducted to test for the effect of initiating a LAI. Offord et al. compared hospitalisations and incidence of relapses by examining large commercial and Medicare health database claims in the United States. Schizophrenia-related admissions were compared 12 months before

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~~Botha et al. analysed in a South African psychiatric population the variables that differentiated a high-frequency user (HFU) and low-frequency user (LFU) of hospital services. Only adult patients with a diagnosis of schizophrenia or schizoaffective disorder were included. High-frequency users were defined as those with multiple admissions to one of the three major tertiary psychiatry hospitals in the Western Cape. They found that being on a LAI was a significant association in the LFU group. However, none of the LFUs were treatment-resistant, which means the HFUs' relapse and readmission rates could be attributed to illness severity rather than treatment efficacy with a LAI. Also of note, both groups had high rates of poor compliance (Botha et al., 2010).~~

#### Motivation for study:

In South Africa there are no known direct studies – case-control studies, mirror-image studies, or randomised controlled studies – comparing the efficacy of LAIs versus OAPs in patients with psychotic spectrum disorders. Such studies could provide evidence in a sample population that can be applied to the local health context of South Africa.

Considering the growing burden of mental illness, and the necessity of utilising resources effectively in South Africa, a mirror-image study that may show that a LAI may decrease hospital admissions and duration of admission is of benefit from the public health point of view – utilisation of resources of the health department, and to influence local prescribing practices. This could potentially result in improving



patients' overall well-being: less time as an inpatient, fewer admissions, fewer psychotic episodes, and more stable periods adapting to, and living in society.

#### Aims and objectives:

The aims and objectives of this mirror-image study are to determine what the effect is when initiating a LAI in patients with psychotic spectrum disorders in a South African population who were previously on OAPs. The primary outcomes will be to compare the number of admissions and durations of admission 12 and 24 months before and after the index admission at which the LAI was first prescribed.

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## Chapter 2: Publication-ready journal manuscript<sup>1</sup>

**Title:** Retrospective observational study: impact of long-acting antipsychotic injectables on hospital admissions

### Abstract

**Background:** The impact on hospitalisation/ relapse rates of utilising long-acting antipsychotic injectables (LAIs) in a South African population suffering from chronic psychotic spectrum mental illness is poorly researched.

**Aim:** To compare the duration and number of hospitalisation episodes 12 and 24 months before and after the initiation of a LAI.

**Setting:** Valkenberg Hospital's adult acute inpatient psychiatry services.

**Method:** This was a retrospective ~~record review using a naturalistic-observational~~ mirror-image study design. Hospitalisation was utilised as a proxy for relapse.

**Results:** Sixty-one patients were identified for the study. A comparison of the 12 months before LAI initiation to the 12 months following LAI initiation showed a reduction in the number of admissions of 44% (55 to 31) and a reduction in the number of inpatient days of 23% (1892 to 1464). There was a statistically significant reduction in the median number of hospital admissions ( $p = 0.005$ ) and median inpatient days ( $p = 0.040$ ).

Comparing the 24 months before to the 24 months following LAI initiation, there was a reduction in the number of admissions of 30% (91 to 64) and inpatient days of 4% (3477 to 3355). There was a statistically significant reduction in the median number of hospital admissions ( $p = 0.014$ ) and a non-statistically significant reduction in median days ( $p = 0.428$ ).

**Conclusion:** The prescription of a LAI reduced the duration and number of hospital admissions over a 12-month period. After 24 months, there were fewer admissions but no significant reduction in the number of inpatient days. This study supports findings of international mirror-image studies.

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<sup>1</sup> Conforms with the South African Journal of Psychiatry's author guidelines – see Appendix 3.

## Introduction

Psychotic disorders like schizophrenia and schizoaffective disorder are severe mental illnesses that are chronic, characterised by multiple relapses throughout the lifespan of a patient. The relapses often lead to repeated hospitalisations with an associated increase in burden of cost, worsening symptoms, impaired functioning, cognitive deterioration and reduced quality of life.<sup>1,2,3</sup> There is no curative management, and symptom relief is the one of the major goals of treatment.

Continuous antipsychotic medication has been shown to improve clinical outcomes and reduce economic burden secondary to reduced relapse and hospitalisation rates, shorter duration of hospitalisation and fewer emergency room visits.<sup>3,4</sup> Poor adherence to antipsychotic medication is one of the most commonly identified significant factors associated with relapse and rehospitalisation, followed by depression and substance abuse.<sup>3,5</sup>

Poor adherence with oral antipsychotics (OAP) is very common and is associated with a ~~much~~ higher chance of relapse.<sup>6</sup> Long-acting antipsychotic injectable (LAI) therapy is a useful alternative treatment option that has comparable and at times superior effectiveness and tolerability of OAP while not requiring daily adherence.<sup>4,7</sup> LAIs may, from a public health perspective, be considered appropriate first-line treatment for schizophrenia.<sup>8</sup> In clinical practice, however, patients and clinicians are sometimes reluctant to use LAIs because of stigma, needle pain, time constraints, side effect concerns, and cost.<sup>9</sup>

The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders states that long-acting intramuscular preparations should be considered for maintenance on the basis of patient preference or convenience, or to manage non-adherence.<sup>10</sup>

The benefit of LAIs over OAPs include improved adherence compared with OAPs.<sup>4,7</sup> They also provide clinicians and caregivers with the opportunity to easily detect non-adherence as the two-weekly or four-weekly dosing is easier to monitor than the oral daily or twice-daily dosing. The injectable also has to be administered by a health professional who can inform carers and mental health care professionals if the patient has missed an injection date. This may allow for an early intervention

regarding adherence challenges before a relapse. This ensured contact with a mental health professional also allows an opportunity for psycho-education. An additional advantage of LAIs is that they have a longer pharmacological half-life than OAPs. This allows a longer period for intervention than OAPs for missed doses before plasma levels drop below critical thresholds, where the risk for relapse, hospitalisation and suicide may be increased.<sup>4</sup>

The evidence for the effectiveness of LAI treatment versus OAP treatment regarding relapse rates is mixed when comparing randomised controlled trials (RCTs) to mirror image studies.

Kishimoto et al.<sup>11</sup> in 2013 published the largest known meta-analysis of mirror-image studies that compared the period before and after initiation of LAI treatment in adults with schizophrenia and schizoaffective disorders. Twenty-five mirror-image studies from 28 countries were included that followed up 5940 patients for at least  $\geq 12$  months ( $\geq 6$  months each on OAP and LAI treatment) and included hospitalisation or relapse-related data.

The results showed strong superiority of LAIs compared to OAP treatment. Specifically, LAIs showed superiority over OAPs in preventing hospitalisation assessed by comparing the risk ratios (number of patients hospitalised divided by number of patients at risk; studies = 16; n = 4066; risk ratio 0.43;  $p < 0.001$ ). Fourteen of the 16 studies specifically showed statistically significant superiority in this outcome measure. LAIs also showed superiority in decreasing the number of hospitalisations assessed by comparing rate ratios (number of hospitalisations divided by the person-years at risk; 15 studies; n = 6342 person-years; rate ratio = 0.38; 95% CI: 0.28–0.51;  $p < 0.001$ ). In a subgroup analysis, LAIs continued to show superiority over OAPs when looking at first-generation antipsychotics (FGA-LAIs) versus second-generation antipsychotics (SGA-LAIs); publication year of studies; study sample size; region; pharmaceutical sponsorship; and data acquisition design in LAI phase.<sup>11</sup>

In 2014 Kishimoto et al.<sup>12</sup> published a meta-analysis of 21 RCTs where LAIs were compared to OAPs in reducing relapses. The meta-analysis included 21 RCTs with 5176 patients. The primary outcome in the meta-analysis was study-defined relapse at the longest time point or, if no definition was available, predominantly psychiatric

hospitalisations were used or, if these were not available, study-defined symptomatic worsening.

The authors showed that LAIs did not reduce relapse compared to OAPs in patients with schizophrenia and schizoaffective disorder. There was also no difference between LAIs and OAPs when considering secondary outcomes: relapse at 3, 6, 12, 18, and 24 months, all-cause discontinuation, discontinuation due to adverse events, drug inefficacy (i.e., relapse and discontinuation due to inefficacy), hospitalisation, and non-adherence. LAIs were not shown to be superior to OAP in subgroup analysis examining medication (FGA versus SGA); publication year; treatment concealment; inpatient versus outpatient status; study duration; medication allocation; and only outpatient studies lasting  $\geq 1$  year.<sup>12</sup>

In South Africa Emsley et al.<sup>13</sup> undertook extensive local research on the treatment of schizophrenia and related psychotic illness with OAP and LAI treatment. They compared the relapse results of an open-label study in which 50 patients were treated with LAI risperidone with the relapse results of a RCT in which 47 patients used oral risperidone and haloperidol. The patients were from Stikland Hospital, a tertiary psychiatry hospital in the Western Cape, and included only those patients with schizophrenia, schizoaffective disorder and schizophreniform disorder. Their findings showed a significantly lower relapse rate in patients on LAI versus OAP.

Botha et al.<sup>14</sup> analysed in a South African psychiatric population the variables that differentiated a high-frequency user (HFU) and low-frequency user (LFU) of hospital services. Only adult patients with a diagnosis of schizophrenia or schizoaffective disorder were included. High frequency users were defined as those with multiple admissions to one of the three major tertiary psychiatry hospitals in the Western Cape. They reported that a LAI prescription was significantly associated with fewer admissions. Of note, both groups had high rates of poor adherence.

In South Africa, there are no known direct studies – case-control studies, mirror-image studies or randomised controlled studies – comparing the efficacy of LAIs versus OAPs in patients with psychotic spectrum disorders. Such studies could provide evidence in a sample population that can be applied to the local health context of South Africa.



This study, therefore, was aimed to determine whether the initiation of a LAI affects the number and duration of hospital admissions for patients who had been diagnosed with schizophrenia or schizoaffective disorder. We compared outcomes for each patient under two conditions: for the time period the patients were prescribed an OAP, and for the time period they were prescribed LAI.

## Research methods and design

This was a retrospective record review using a mirror-image study design. The mirror point was set as the entire admission in which the LAI was prescribed. Index admission days for both oral antipsychotics and LAIs were excluded from the mirror point.

The study was conducted in Valkenberg Hospital, one of the tertiary psychiatric hospitals in the Western Cape, South Africa. It was approved by the University of Cape Town Human Research Ethics Committee and the National Health Research Database. All collected data was kept anonymous.

### Key inclusion criteria

~~The electronic records on Clinicom Information Management System of adult~~

1. Adult male and female patients, admitted to acute inpatient psychiatric services between 01 January 2013 and 31 December 2013 were screened.

2. Those that had been initiated and discharged on a LAI were selected. Their electronic records were checked to see whether they had been prescribed only OAPs in the 24 months prior to the LAI prescription, and that they continued to be prescribed the LAI 24 months after.

3. Only patients with a Diagnosis of schizophrenia or schizoaffective disorder were included.

### Key exclusion criteria

No type of LAI or OAP were excluded.

~~Patients were excluded if they had been~~ 1. D diagnosed and treated within 24 months of the prescription of the LAI (including first-episode psychosis);

~~2. had been to the~~ Valkenberg forensic observation or psychotherapeutic services; ~~or~~  
were

3. ~~R~~ Referred from or discharged to another province or private psychiatric services outside the catchment area of Valkenberg Hospital.

Patients who had a forensic admission or therapeutic admission during any time in the study period were excluded. The reasons were that a forensic admission is a set time period of observation of 30 days where patients are not admitted for a relapse of their mental illness, but for a court-appointed assessment. Likewise, the therapeutic admission is a set period and the admission into the unit is not based on relapse, but for psychotherapeutic reasons. This set period of time for possible non-relapse-related admissions may have biased our results and were therefore excluded.

The decision to exclude Assertive Community Treatment (ACT) team patients was based on the premise that ACT team patients are not treatment as usual. They involve home visits with a dedicated multidisciplinary team. Patients are selected with multiple previous admissions (>3 admissions in one year) to Valkenberg Hospital and are often prescribed LAI. The exclusion of ACT team patients reduced the number of potential patients in our study.

~~The mirror point was set as the entire admission in which the LAI was prescribed.~~

### **Data collection**

The electronic records on Clinicom Information Management System of adult male and female patients, admitted to acute inpatient psychiatric services between 01 January 2013 and 31 December 2013 were screened.

Those that had been initiated and discharged on a LAI were selected. Their electronic records were checked to see whether they had been prescribed only OAPs in the 24 months prior to the LAI prescription, and that they continued to be prescribed the LAI 24 months after.

A range of clinical and demographic information was collected including: age; sex; primary diagnosis; comorbid psychiatry diagnosis; substances used; LAI (name, dosage, and dosing schedule); and co-prescribed psychotropic medication.

The number of psychiatric-related admissions and the duration of psychiatric-related admissions were recorded for 12 and 24 months before and after the admission during which the LAI was prescribed. Psychiatric admissions to district hospitals were also included.

The **primary** outcomes were the number of admissions, and the duration of admissions.

### **Data analysis**

Data was analysed using STATA version 13.

Initially, categories were formed in order to characterise the outcome distributions as follows: numbers of admissions were categorised into 0, 1, 2 and 3 or more visits and durations into less than 1 month (31.5 days), 1 month (<2 months), 2 months <3 months, 3 or more months. Thereafter, means (95% confidence intervals [CIs]), medians (interquartile range [IQR]) and totals for admissions were calculated for the outcomes and for the differences in outcomes between pre- and post-LAI periods.

The distributions of the number of admissions and the duration of inpatient admission days were examined using histograms and tested for normality using Shapiro Wilks tests. Log-transformations of non-zero data were attempted to approximate normal distributions, but were not successful in achieving this.

Wilcoxon signed-rank tests for paired observations were therefore used to compare significant differences in median values and distributions for pre- and post-LAI periods.

## **Results**

### **Demographic and clinical data**

A total of 61 **participants were eligible for inclusion, subjects were identified**. The average age was 35 years old and the majority of subjects were male (74%). Most of the subjects had a diagnosis of schizophrenia (75%) and the most commonly prescribed LAI was zuclopenthixol decanoate (50%). Forty-nine percent of the subjects had recorded usage of one or more substances that included methamphetamine, cannabis, alcohol, cocaine or methaqualone. Five percent of subjects were prescribed only a LAI on discharge from the admission in which the

LAI was initiated while 43% were co-prescribed an OAP; 3% co-prescribed a mood agent and 49% co-prescribed an OAP and mood agent. See Table 1.

**TABLE 1: Demographics and clinical data of participants (n = 61).**

|  |           |
|--|-----------|
| <b>Age (years)</b>                     |           |
| Mean (SD)                              | 35 (10.4) |
| Range                                  | 20-58     |
| <b>Gender</b>                          |           |
| Male                                   | 45 (74%)  |
| Female                                 | 16 (26%)  |
| <b>Diagnosis</b>                       |           |
| Schizophrenia                          | 46 (75%)  |
| Schizoaffective disorder               | 15 (25%)  |
| <b>Comorbid Substance Use Disorder</b> |           |
| Not specified                          | 31 (51%)  |
| Cannabis+/- Methamphetamine+/- other   | 30 (49%)  |
| <b>LAI</b>                             |           |
| flupenthixol decanoate                 | 18 (30%)  |
| fluphenazine decanoate                 | 12 (20%)  |
| zuclopenthixol decanoate               | 31 (50%)  |
| <b>Co-prescribed psychotropic</b>      |           |
| Nil (LAI only)                         | 3 (5%)    |
| Oral Antipsychotic*                    | 26 (43%)  |
| Oral Mood agents **                    | 2 (3%)    |
| Oral Antipsychotic and Mood agents     | 30 (49%)  |

\* antipsychotic = haloperidol, trifluoperazine, chlorpromazine, olanzapine, risperidone, amisulpride.

\*\* mood agents = sodium valproate, lithium, citalopram.

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## 12 months pre- and post-LAI

When comparing the 12 months before LAI initiation to the 12 months following LAI initiation (see Table 2), there was a reduction in the number of admissions of 24 admissions (55 to 31) and number of inpatient days of 428 days (1892 to 1464). The decrease was not statistically significant due to the wide 95% confidence intervals. There was a statistically significant reduction in the median number of hospital admissions and median number of inpatient days.

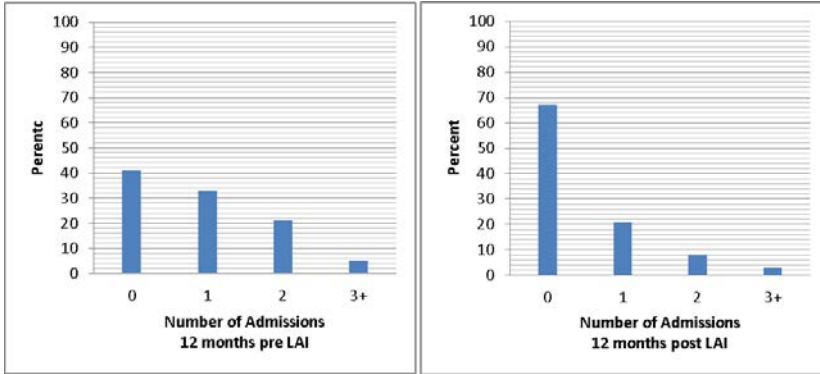
Figures 1 and 2 demonstrate the skewed distribution of the number of admissions and duration of admissions.

**TABLE 2: Summary of differences for 12 months pre- and post-LAI (n = 61)**

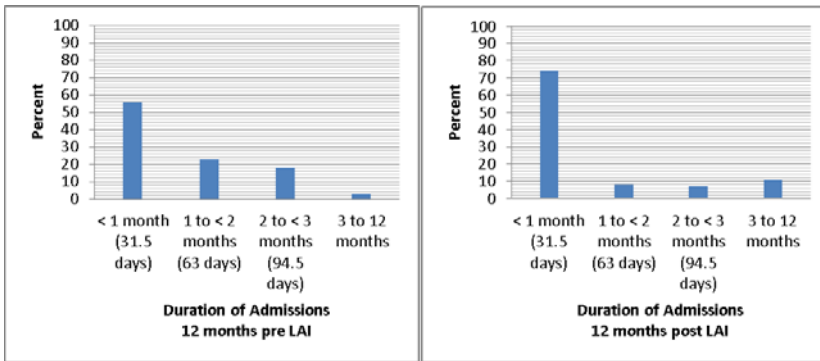
|                      | Number of admissions pre LAI: 12 months       | Number of admissions post LAI: 12 months       | Difference           | p-value             |
|----------------------|---|--|----------------------|---------------------|
| <b>Mean (95% CI)</b> | 0.9 (0.7-1.1)                                 | 0.5 (0.3-0.7)                                  | 0.4 (0.1-0.7)        | N/A                 |
| <b>Median (IQR)</b>  | 1 (0-2)                                       | 0 (0-1)  | 0 (0-1)              | *Z=2.780<br>p=0.005 |
| <b>Total</b>         | 55  | 31   | 24 (6.1-42.7)**      |                     |
|                      | Admission duration in days pre LAI: 12 months | Admission duration in days post LAI: 12 months | Difference           | p-value             |
| <b>Mean (95% CI)</b> | 31 (22-40)                                    | 24 (12-36)                                     | 7 (-5 to 19)         | N/A                 |
| <b>Median (IQR)</b>  | 16 (0-54)                                     | 0 (0-33)                                       | 0 (0-33)             | *Z=2.050<br>p=0.040 |
| <b>Total</b>         | 1892  | 1464   | 428 (-305 to 1159)** |                     |

\* Wilcoxon matched pairs-signed rank test.

\*\*95% CI for difference is based on 95% CI of mean. Mean is known to be skewed.



**FIGURE 1: Number of admissions 12 months pre- and post-LAI.**



**FIGURE 2: Duration of admissions 12 months pre- and post-LAI.**

### 24 months pre- and post-LAI

Comparing the 24 months before LAI initiation to the 24 months following the LAI initiation (see Table 3), there was a reduction in the number of admissions of 30% (91 to 64) and number of inpatient days of 4% (3477 to 3355). The decrease is not statistically significant due to the wide 95% confidence intervals. There was also a statistically significant reduction in the median number of hospital admissions and a non-statistically significant reduction in inpatient hospital admission.

Figures 3 and 4 demonstrate the skewed distribution of the number of admissions and duration of admissions.

**TABLE 3: Summary of differences for 24 months pre- and post-LAI for all participants (n = 61).**

|                     | Number of admissions pre LAI: 24 months       | Number of admissions post LAI: 24 months       | Difference            | p-value             |
|---------------------|---|--|-----------------------|---------------------|
| <b>Mean (Range)</b> | 1.5 (1.1-1.8)                                 | 1.0 (0.6-1.5)                                  | 0.4 (0.0-0.9)         |                     |
| <b>Median (IQR)</b> | 1 (1-2)                                       | 1 (1-1)  | 0 (0-1)               | *Z=2.457<br>p=0.014 |
| <b>Total</b>        | 91  | 64   | 27 (0-53)**           |                     |
|                     | Admission duration in days pre LAI: 24 months | Admission duration in days post LAI: 24 months | Difference            | p-value             |
| <b>Mean (Range)</b> | 57 (39-75)                                    | 55 (31-79)                                     | 2 (-22 to 26)         |                     |
| <b>Median (IQR)</b> | 46 (0-78)                                     | 8 (0-61)                                       | 1 (-34 to 37)         | *Z=0.792<br>p=0.428 |
| <b>Total</b>        | 3477  | 3356   | 121 (-2074 to 2257)** |                     |

\* Wilcoxon matched pairs signed rank test.

\*\* 95% CI for difference is based on 95% CI of mean. Mean is known to be skewed.)

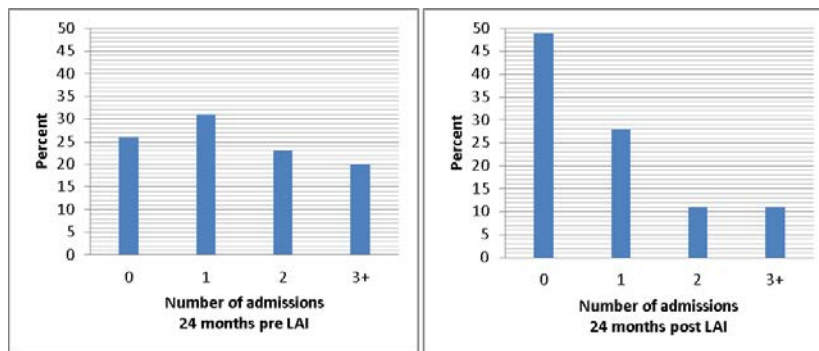
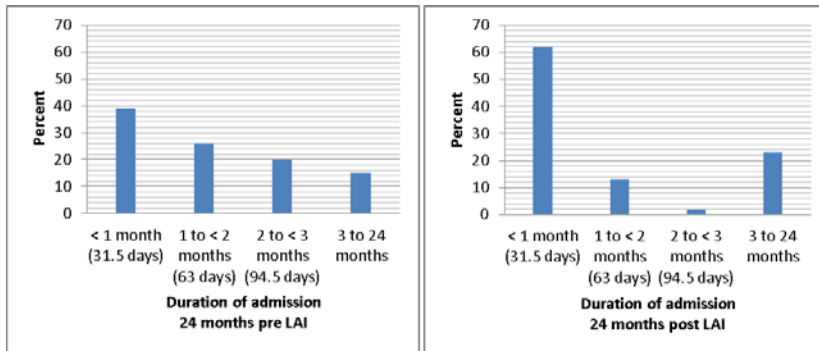


FIGURE 3: Number of admissions 24 months pre- and post-LAI.



**FIGURE 4: Duration of admissions 24 months pre- and post-LAI.**

## Discussion

**Main findings:** In our cohort of 61 patients, there was a reduction in the number of psychiatric admissions and duration of hospital admissions when comparing the 12- and 24-month period before and after the initiation of a long-acting antipsychotic injectable depot.

Statistically significant reductions were noted for the median number of admissions and median number of inpatient days in the 12-month mirror period and the median number of admissions in the 24-month mirror period.

Reductions were observed for the median number of inpatient days in the 24-month mirror period, but these were not statistically significant.

~~This may be explained by the larger spread of the distribution in the post 24 month LAI group versus the pre 24 month group or that, by 24 months, there were fewer but longer admissions as a result of severity of relapse.~~

**Concordance with other literature:** Our results are in keeping with the largest published meta-analysis of mirror-image studies where strong superiority of LAIs compared to OAPs was shown in decreasing the number of hospitalisations and reducing hospitalisation days in patients with schizophrenia and schizoaffective disorder.<sup>11</sup>

However, direct comparison is difficult as the meta-analysis mirror-image study utilised both first-generation antipsychotic LAI and second-generation antipsychotic



LAI, while our study only considered FGA-LAI. Also, the comparison between the pre-LAI and post-LAI arms were calculated as risk ratios in the meta-analysis, whereas our study utilised medians due to the widely skewed distribution of the data.

Furthermore, the mean number of patients per study included in the meta-analysis was 235 patients (range: 24 – 2300) compared to our cohort of 61. Convenience sampling was used for our study and in future studies we recommend increasing the window period of admissions to increase the cohort and thereby improve the reliability of results.

Our results differ from the negative findings of a meta-analysis of randomised controlled trials that compared LAI and OAP.<sup>12</sup> The difference may be explained as follows: the participants in RCTs have to give informed consent and therefore may be less unwell than those in mirror-image studies. They may also have better engagement with health care providers; better adherence to the treatment; lower illness severity (particularly with increasing stringency of consent processes), and better cognitive capabilities to understand complex issues. In addition, participation in a controlled trial alters the natural ecology of treatment delivery and experience, including receiving more, and different types, of attention. More frequent monitoring during a trial also enables psychiatrists to change dosages according to the symptoms and provide supportive counselling. The naturalistic setting of a mirror-image study is more in keeping with real life clinical scenarios and hence better able to reflect real-world impacts of LAI treatment.<sup>12, 15</sup>

The choice of the mirror point is an important consideration as it may favour the LAI or the OAP. By placing the mirror point at the date of initiation of the LAI, it would favour the OAP arm as admission days that should be attributed to the OAP phase will be attributed to the LAI arm. Some studies have opted to place the mirror point two weeks after the initiation of the LAI to correct this. Our choice was to remove the index admission days from both OAP and LAI arms. This could have potentially favoured the LAI arm as admission days due to failure of the OAP were excluded. However, it also removed admission days from the LAI that were not related to failure of the LAI. This meant that the index days could be attributed to either arm. The length of the index admission is also affected by other non-related variables such as severity of illness, bed shortage/ pressure and unfavourable home

circumstances. None of these factors reflect on the efficacy of the antipsychotic treatment choice. In future studies, we recommend using several mirror-image points during analysis to determine the effects of the different points on results.

Co-morbid substance use: Approximately half of the sample had recorded usage of substances in various combinations of polysubstance use, including methamphetamine, cannabis, methaqualone, heroin and alcohol. It was noted that the diagnosis of substance-use disorders was made for only one patient. The recording of substances was also not uniform. In those whom the discharge summary did not specifically mention use of substances, it was recorded as 'not specified'. Considering the high prevalence of comorbid substance-use disorders in South Africa and its role in relapses, it is likely our results regarding substance use are an underestimate.

Polypharmacy: The use of antipsychotic polypharmacy is generally not advocated. However, only 3% of patients were discharged on a LAI only. This might be accounted for by the prescribing practice of initially stabilising patients on their previously prescribed OAP, initiate a LAI, and then cross-titrate, which may require 3–6 months to reach a steady state. The OAP would then be tapered and stopped. Our results may reflect that cross-titration and stopping the OAP is done post-discharge at community health service facilities. The use of mood agents in 49% of the sample indicates the high prevalence of comorbid mood disorders like anxiety and depression.

Limitations: Possible inherent biases of this mirror-image study include expectation and conservative bias: those patients started on a LAI were done so presumably because of a poor response to the OAP or were more severely ill than with patients receiving OAPs. Also, if a patient is known to be on a LAI, then adherence is assumed to be adequate, which may influence the clinician's decision to readmit.

The utilisation of hospital admissions as a proxy for relapse is a common and useful method in research studies.<sup>11</sup> As a proxy, however, it has limitations as the reasons for hospitalisation are multi-factorial. These factors include poor adherence, life stressors, poor social support, natural course of illness, clinical practice of the admitting clinicians regarding their threshold before admitting, and bed availability/bed shortages within the hospital.<sup>3</sup>

~~Only 49% of the sample had recorded usage of substances in various combinations of polysubstance use, including methamphetamine, cannabis, methaqualone, heroin and alcohol. It was noted that the diagnosis of substance use disorders was made for only one patient. The recording of substances was also not uniform. In those whom the discharge summary did not specifically mention use of substances, it was recorded as 'not specified'. Considering the high prevalence of comorbid substance use disorders in South Africa and its role in relapses, it is likely our results regarding substance use are an underestimate.~~

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The number of patients lost to follow-up remains unknown. The readmission data was obtained from an electronic system called Clinicom Information Management system. This system is limited to the Western Cape and includes only district hospitals and tertiary psychiatry hospitals. Any admissions to health services in private practice or outside the Western Cape were not captured. A patient may have no admissions after the initiation of the LAI, but this may be due to the patient having relocated to another province or private practice.

The pharmacy data of when psychotropic medication were collected by a patient or administered to a patient at their local community clinic, district hospital and Valkenberg Hospital is not available in a central database. Therefore, actual adherence rates in respect of OAP or LAI are unknown. Future studies would benefit from centrally located databases that record patient' visits, admissions, medication, collection of medication in all provinces, and also within the private sector. This would allow corroborating the presumed increased adherence rates of LAI.

Patients who had a forensic admission or therapeutic admission during any time in the study period were excluded. The reasons were that a forensic admission is a set

time period of observation of 30 days where patients are not admitted for a relapse of their mental illness, but for a court-appointed assessment. Likewise, the therapeutic admission is a set period and the admission into the unit is not based on relapse, but for psychotherapeutic reasons. This set period of time for possible non-relapse-related admissions may have biased our results and were therefore excluded.

The decision to exclude Assertive Community Treatment (ACT) team patients was based on the premise that ACT team patients are not treatment as usual. They involve home visits with a dedicated multidisciplinary team. Patients are selected with multiple previous admissions (>3 admissions in one year) to Valkenberg Hospital and are often prescribed LAI. The exclusion of ACT team patients reduced the number of potential patients in our study. It was noted, however, that several patients were included in the study that had sufficient previous admissions to be suitable for the ACT team (likely reasons being that the ACT team was at capacity, the patient lived in an area not serviced by the ACT team, or the patient was not referred to the ACT team). These patients had a larger number of admissions pre- and post-LAI than the mean of the sample, and skewed our results significantly.

Other limitations that should be addressed in future studies are the inclusion of a control group (a matched population sample that receives only OAPs over the whole study period), as well as taking note of the differences in adverse effects between the LAI and OAP arms of such studies.

## **Conclusion**

The demonstrated benefit does suggest that LAI plays an important role in the management of chronic psychotic spectrum disorders in the South African public sector. Our results demonstrated a reduction in number of hospital admissions and inpatient days in the 12- and 24-month period after the initiation of a long acting injectable depot. This is in keeping with international mirror-image studies. [In view of the growing burden of mental illness in the context of inadequate resources, this study's finding support the use of LAI as an intervention to optimise the limited resources available in the South African Mental Health sector.](#) However, in view of the small sample size, limitations of the study design and the non-significant

reduction in inpatient days over 24 months, we advise that the results should be treated with caution.

Recommendations: In future studies we recommend increasing the window period of admissions to increase the cohort and thereby improve the reliability of results; using several mirror-image points during analysis to determine the effects of the different points on results. Future studies would also benefit from centrally located databases that record patient' visits, admissions, medication, collection of medication in all provinces, and also within the private sector. This would allow corroborating the presumed increased adherence rates of LAI inclusion of a control group (a matched population sample that receives only OAPs over the whole study period), as well as taking note of the differences in adverse effects between the LAI and OAP arms of such studies

## **Acknowledgements**

I would like to acknowledge the following people: Ms Deborah Constant for statistical analysis support; Mr William Maseburi for statistical analysis support; Dr Neil Horn in his capacity as supervisor and Dr Peter Williams-Ashman in his capacity as co-supervisor.

## **Competing interests**

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

## **Authors' contributions**

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## Appendix 1: Data sheet

|  |  |
|--|--|
| Study number: allocated sequentially from 001 to 100   |  |
| Date of birth  |  |
| Age  |  |
| Sex  |  |
| Primary diagnosis                                      |  |
| Comorbid psychiatry diagnosis                          |  |
| Substances used  |  |
| LAI (name, dosage, dosing schedule)                    |  |
| Co-prescribed Psychotropic Medication                  |  |
| Name of sub district (referred from and discharged to) |  |
| Date of admission                                      |  |
| Date of discharge                                      |  |
| Dates of admissions in previous 24 months              |  |
| Dates of admissions in post 24 months                  |  |



**Appendix 2: University of Cape Town, Faculty of  
Health Sciences, Human Research Ethics Committee  
approval letter**

**Appendix 3: Instructions to authors submitting  
articles to the South African Journal of Psychiatry**