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Olanzapine long-acting injection, discontinuation rates and reasons for discontinuation: 10 years' experience at a UK high-secure hospital

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Azizah Attard, John Wakelam, Josephine Broyd, David Taylor and Jonathan Hafferty

Abstract

Background: Olanzapine pamoate has been shown to be an effective second-generation long-acting injection. Its popularity has possibly been adversely affected by the rare incidence of post-injection syndrome (PIS) and the associated requirement to monitor for 3 h after each injection.

Objective: This study aimed to collect and present data on the use of olanzapine long-acting injection (OLAI) over a 10-year period in a high-security forensic hospital in South East England.

Design: This was a non-interventional retrospective study collecting information from anonymised electronic patient and prescription records. As per hospital Trust guidelines, patient consent to access of hospital records was presumed unless explicitly withdrawn.

Method: All patients prescribed OLAI between the years 2009 and 2019 were identified. Data collected included date that OLAI was started, stopped, dose range, side effects and concomitant medication.

Results: Of 88 patients who were started OLAI, 45 (51%) continued at month 24. At 60 months, 22 of 70 (31%) patients for whom data were available continued with OLAI. Over 60% of continuers were on higher than recommended doses. Of almost 5000 injections administered, there was 1 episode of PIS.

Conclusion: OLAI is an effective treatment for schizophrenia and schizoaffective disorder, especially when used in patients have been able to tolerate the drug and were stabilised on it for 24 months. In over half the patients who continued OLAI, the doses were higher than that recommended by the manufacturer. The incidence of PIS in this study was very low in comparison with other studies.

Registration code: 2049

Keywords: amtipsychotic, continuation, depot, olanzapine, schizophrenia

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Correspondence to:
Azizah Attard
Pharmacy Department, West London NHS Trust, 1 Armstrong Way, Southall, London UB1 3EU, UK.
azizah.attard2@nhs.net

John Wakelam
Pharmacy Department, West London NHS Trust, London, UK

Josephine Broyd
West London NHS Trust, London, UK

David Taylor
Pharmacy Department, South London and Maudsley NHS Foundation Trust, London, UK

Jonathan Hafferty
Broadmoor Hospital, West London NHS Trust, London, UK

Introduction

Poor adherence to antipsychotic therapy can be as high as 50% and is associated with risk of relapse and hospitalisation.[1] Long-acting antipsychotic injections are administered at defined intervals assisting healthcare professionals in managing poor adherence.[2–4] However, they have often been regarded with negativity by both patients and medical professionals, with perceptions of coerciveness and diminished development of therapeutic relationships.[5–7] Even with the development of second-generation long-acting antipsychotics, LAIs remain arguably under-utilised.[8]

Oral olanzapine is well established as an effective treatment for schizophrenia.[9] The olanzapine long-acting injection (OLAI) is associated with post-injection syndrome (PIS) in 0.1% of patients. PIS possibly occurs through intravasation leading to olanzapine levels as high as 600 μg/L (range, 20–40 μg/L), and although there have not been any associated fatalities, it can cause delirium, somnolence and lead to intubation.[10–12] The requirement for 3 h post-injection monitoring undoubtedly restricts OLAI use and the observation that 'olanzapine depot may be very difficult to administer to those patients who need it the most'.[13]

Broadmoor Hospital is a 200-bed high-security forensic hospital serving the population of South East England. The average length of stay is 5.3 years and the level of nursing input is high. In 2014, Baruch *et al.* demonstrated the efficacy of OLAI in reducing violence in Broadmoor Hospital patients. In this study, we aim to provide a long-term perspective on measures of tolerability, adherence, and rates of discontinuation for OLAI through analysis of up to 10 years of patient healthcare record data.[14]

Methods

This study was approved by the High Secure Medicines Advisory Committee in June 2021 code: 2049. As per hospital Trust guidelines, patient consent to access of hospital records was presumed unless explicitly withdrawn. This was a non-interventional retrospective study collecting information from electronic patient and prescription records. Data were collected and viewed by staff directly involved with patient care from the pharmacy and hospital departments. Patient data were fully anonymised and any identifiable data removed.

All patients prescribed OLAI between the years 2009 and 2019 were identified. Data collected included patient demographics, medication history, number of injections, time between injections, adverse effects, antipsychotic immediately before OLAI, concomitant medications, discontinuation reasons and antipsychotic immediately after OLAI. All patients had been prescribed OLAI for at least 24 months and followed up till 60 months. Discontinuation was defined as not receiving the OLAI at the next scheduled dose. The date of discontinuation was defined as the date the next dose was due or date of death.

Data on doses used at the beginning of the study and doses used for patients who continued on OLAI were also collected.

Statistical analysis

Baseline characteristics are summarised using descriptions commonly used in UK national census. Statistical analysis was carried out using SPSS 27.01. which allowed for the development of the Kaplan–Meier plots were produced to analyse discontinuation rates. The plots have been censored to report where a patient was lost to follow-up or we had incomplete observations. This method of analysis allows us to share data as a comparative plot or curve rather than single isolated points in time.

Results

Patient demographics

A total of 103 patients had been prescribed OLAI between the years 2009 and 2019, after applying the inclusion criteria (see Figure 1); 88 patients were retained and had a primary diagnosis of schizophrenia, schizoaffective and bipolar disorder. Patient demographics and clinical information for the retained patients are summarised in Table 1.

Continuation

At 24 months, 45 patients (51%) continued with OLAI as expressed in the Kaplan–Meier curve (Figure 2).

Of the 43 that discontinued medication, the largest number 18 (42%) were switched to clozapine (Table 2) while 13 (30%) were switched to a different long-acting injection (Table 3). There were also 2 (4%) patients who continued with OLAI that prescribed a combination of depot antipsychotic therapy; the combinations were OLAI and Zuclopenthixol LAI ($n = 1$) OLAI and Flupenthixol LAI ($n = 1$).

The main reason documented for OLAI discontinuation at 24 months was perceived ineffectiveness (21 [49%]) (Table 4). Of the 43 patients who discontinued therapy, 2 (5%) discontinued to prepare for discharge as the unit they were being discharged too were unable to facilitate PIS monitoring.

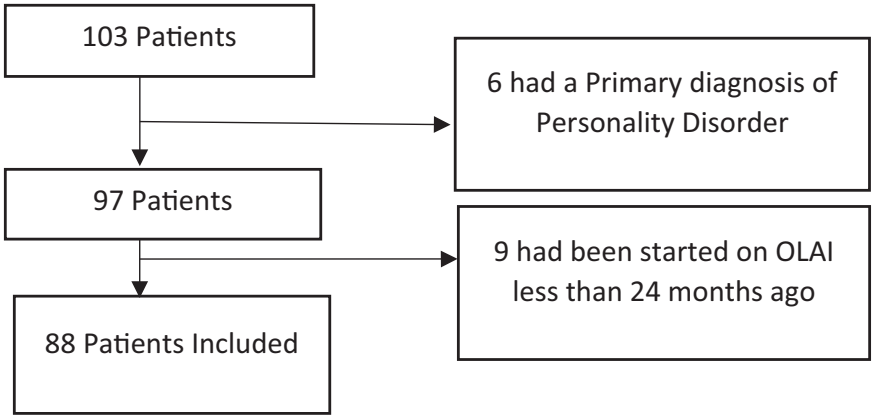


Figure 1. Inclusion criteria.

Figure 3 follows up the original patients until discontinued or until the time of data collection. At 60 months, of 88 patients 70 were followed up and 22 (31%) continued with OLAI.

Between months 24 to 60 of the original patients, if we were to follow up only the remaining 45 patients, at 60 months we had data for 27 patients and 22 (81%) continued with therapy (see Figure 4).

OLAI doses at initiation and continuers on are presented in Table 5.

According to the summary of product of characteristics, the maximum dose of OLAI is 300 mg every 2 weeks. Of the 88 patients who started the study, 6 patients (7%) were prescribed higher than these doses: 300 mg every 10 days ($n = 1$), 405 mg every 10 days ($n = 1$) and 405 mg every 2 weeks ($n = 4$). Of those who continued with OLAI at 24 months, 27 (60%) were prescribed higher than the maximum dose: 300 mg every 10 days ($n = 1$), 405 mg every 10 days ($n = 17$) and 405 mg every 2 weeks ($n = 9$).

Adverse effects

In total, 4995 OLAI doses were given over 10 years. In that time, one (0.02%) serious adverse effect of PIS was noted. Of 88 patients, 28 (32%) were at some point also prescribed concomitant medication for diabetes, obesity and raised cholesterol. In the group of continuers, 19 patients (42%) were prescribed these concomitant medications, 4 patients (9%) were on the medication before OLAI and 4 patients (9%) were able to stop these medications. In the group of discontinuers, 9 patients (21%) were prescribed these concomitant medications, 2 patients (5%) were prescribed these before OLAI and 3 patients (7%) were able to stop these medications.

Discussion

From 88 patients, 45 (51%) continued with OLAI at 24 months. At 60 months, data for 70 patients were available and 22 (31%) continued OLAI. In 10 years, 4995 OLAI doses were given. In that time, one (0.02%) serious adverse effect of PIS was noted. This patient had been receiving the injection at the dose prescribed for 8 years, administered in the usual site by the usual nurse before suffering PIS 15–20 min post injection. He fully recovered within 48 h and remains on the medication at the same dose at the time of writing, some 9 months later. The incidence of concomitant medication for diabetes, obesity and hypercholesterolemia is similar to other studies on weight gain and was proportional to the dose of oral and OLAI used.[15]

If we were to summarise results of studies on the relative efficacy and clinical effectiveness of non-clozapine second-generation antipsychotics (SGA) and first-generation antipsychotics (FGA), olanzapine is marginally more effective than aripiprazole, risperidone, quetiapine and ziprasidone; olanzapine has also been shown to be of more effective in comparison with FGAs.[16,17] The effectiveness of olanzapine in the treatment of schizophrenia is indirectly shown by its extensive clinical use and is exemplified by studies such as CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) which showed olanzapine had the lowest discontinuation rate when compared with five other

Table 1. Baseline characteristics.[a,b,c]

Characteristics	Total
	***n* = 88**
Age (years)	
Mean, SD	35.5, 8.8
Min, max	18, 59
	***n* (%)**
Ethnicity	
Asian/Asian British	6 (6.8)
Black/Black British	35 (39.8)
Mixed background	8 (9.1)
Other	3 (3.4)
White	36 (40.9)
Diagnosis (all)[b]	
Paranoid schizophrenia	66 (75)
Schizoaffective disorder	18 (20.5)
Hebephrenic schizophrenia	2 (2.3)
Bipolar disorder	2 (2.3)
Anxiety disorder	1 (1.1)
Post-traumatic stress disorder	1 (1.1)
Dissocial personality disorder	30 (34.1)
Emotionally unstable personality disorder	5 (5.7)
Paranoid personality disorder	2 (2.3)
Mixed personality disorder	7 (8.0)
Personality disorder (unspecified)	3 (3.4)
Mental and behavioural disorders due to drugs or alcohol	17 (19.3)
ADHD	4 (4.5)
Autism spectrum disorder	3 (3.4)
Diagnosis under review	1 (1.1)

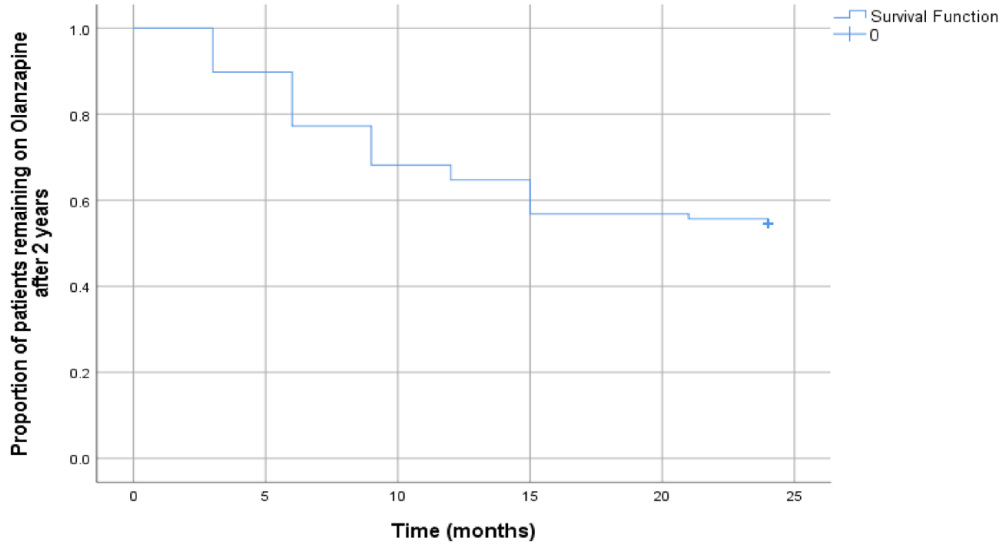
ADHD, attention-deficit/hyperactivity disorder.
[a]All patients included identified as being male.
[b]Diagnostic Nomenclature from ICD10 (International Statistical Classification of Diseases and Related Health Problems, 10th Edition) that was used in Patient Electronic Notes.
[c]Diagnosis was not mutually exclusive.

antipsychotic drugs, over an 18-month treatment period.[18] It is important therefore to be able to offer olanzapine as a treatment option in a different formulation. A perceived disadvantage of LAIs in general is slow dose titration and a protracted time to reach steady state; in practice, however, the time taken to reach therapeutic efficacy is often less than the time taken to steady state.[19] Such perceptions can often lead to prescribing challenges in acutely disturbed patients, for example, where rapid dose adjustments are felt necessary. Such scenarios can lead to confusing regimes with altered dosing, administration interval or the use of 'top-up' oral medication being prescribed.[5] The OLAI formulation addresses many of these challenges; peak plasma levels are seen within 2–7 days and efficacy is demonstrated as early as 3 days.[20,21]

In this study, 27 (60%) patients were prescribed higher than recommended OLAI doses by the manufacturer. This figure is broadly similar to that in another study which found a long time to all cause discontinuation, at 24 weeks, when patients were randomised to receive 'medium' to 'high' doses of OLAI.[15] Further evidence supporting the need for higher OLAI doses comes from a positron emission tomography (PET) in which 14 patients were treated with OLAI 300 mg every 4 weeks for 6 months. It was found that oral supplementation was needed in half the patients for the first 4 months.[22] The authors concluded that this could indicate that oral supplementation of olanzapine or a higher dose or frequency of injections could be required.[22]

It is notable that secondary care community mental health services refused to accept two patients (5%) prescribed OLAI at discharge from inpatient care, as they were not able to provide the required 3 h PIS monitoring, giving the clinician no option but to discontinue the otherwise effective OLAI. As discussed, the incidence of PIS is reported as less than 0.1% in the Summary of Product Characteristics, supported by a study reporting a rate of 0.044%.[23]

Patients suffering from schizophrenia prescribed FGA continue with their LAI formulation for a longer period compared with the same drug in an oral formulation.[24,25] In SGA continuation studies, 16% of 211 patients continued risperidone LAI after 3 years.[26] At 2 years, 42% of 225 patients



Text (data)

N continuing	88	79	68	60	56	49	49	48	45
% continuing	100	90	77	68	64	56	56	55	51
Months	0	3	6	9	12	15	18	21	24

Figure 2. Kaplan–Meier curve for patients remaining on olanzapine after 2 years ($n = 88$).

Table 2. Antipsychotic prescribed immediately before and after OLAI treatment episode.

	Antipsychotic switched from $N = 88$	**Antipsychotic switched to $N = 43$**
Amisulpride oral	0	2
Aripiprazole oral	2	0
Clozapine oral	16	18
Olanzapine oral	39	8
Risperidone oral	4	1
Quetiapine oral	5	1
Aripiprazole LAI	1	2
Flupenthixol LAI	3	2
Fluphenazine LAI	1	0
Haloperidol LAI	3	2
Paliperidone LAI	2	5
Risperidone LAI	0	1
Zuclopenthixol LAI	12	1

LAI, long-acting injection; OLAI, olanzapine long-acting injection.

Table 3. Route of administration of antipsychotic immediately before and after OLAI treatment episode.

Routes of Administration	Switched from *N* = 88	Switched to *N* = 43
LAI	22 (25%)	13 (30%)
ORAL	66 (75%)	30 (70%)

LAI, long-acting injection; OLAI, olanzapine long-acting injection.

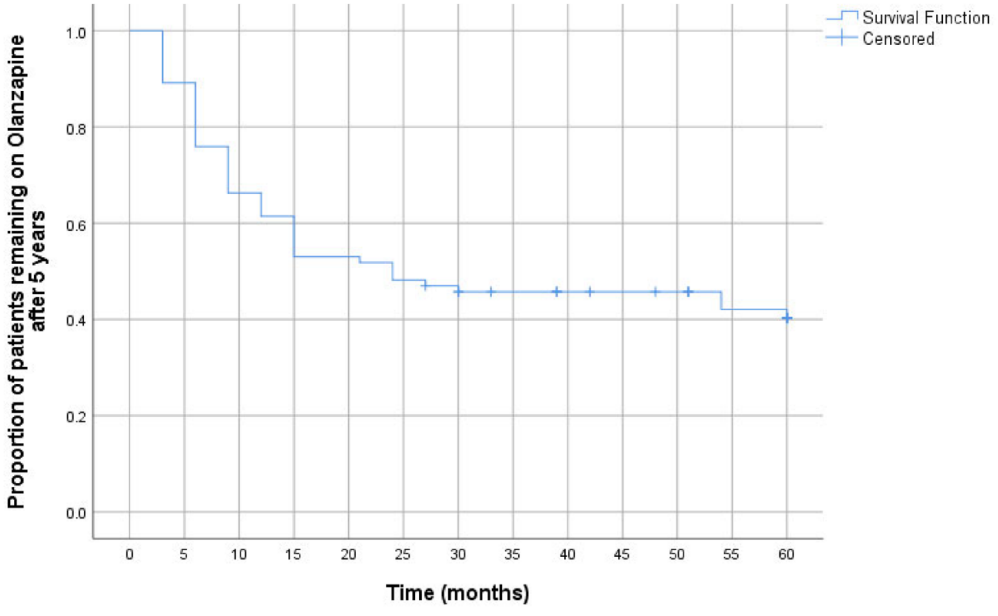
Table 4. Reasons for discontinuation of OLAI.

Reasons for Discontinuation *n* = 43	Numbers
Ineffective	21
Intolerance	13
Patient decision	4
Non-concordant	3
Discharged to a different unit	2

OLAI, olanzapine long-acting injection.

prescribed monthly paliperidone LAI continued their medication and 60% of 111 patients prescribed 3-monthly paliperidone LAI continued with their medication.[27,28] The authors of the 3 monthly LAI study attributed the better rates to patients having been previously stable on monthly Paliperidone. We add to this information, reporting OLAI continuation at 2 years as 51% of 88 patients and at 60 months as 31% of 70 patients.

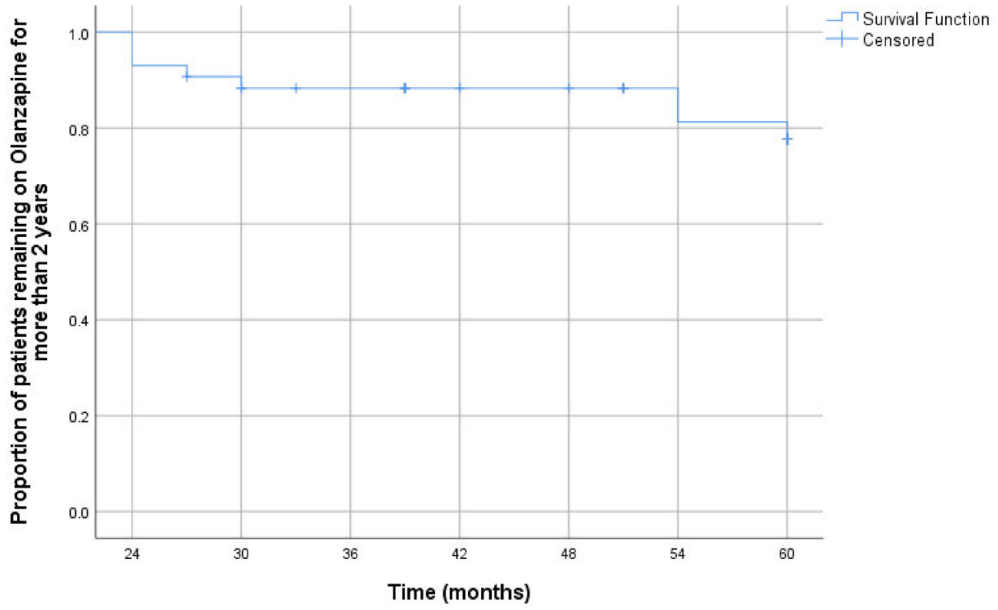
Adherence behaviour that changes and fluctuates over time is largely considered a core aspect of schizophrenia and should be considered when



Text (data)

Total Patients	**(N)**	88	88	88	88	88	88	88	88	88	87	85	82	82	79	77	77	76	73	72	71	70
Patients prescribed OLAI	**(N)**	88	79	68	60	56	49	49	48	45	43	40	37	37	32	31	31	30	26	24	23	22
% Continuing		100	90	77	68	64	56	56	55	51	49	47	45	45	41	40	40	39	36	33	32	31
Months		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60

Figure 3. Kaplan–Meier curve for patients remaining on OLAI for 5 years (n = 88).



Total Patients	N	45	44	42	39	39	36	34	34	33	30	29	28	27
Patients prescribed OLAI (N)		45	43	40	37	37	32	31	31	30	26	24	23	22
% Continuing		100	98	95	95	95	89	91	91	91	87	83	82	81
Months		24	27	30	33	36	39	42	45	48	51	54	57	60

Figure 4. Kaplan–Meier curve for the same patients continuing OLAI between months 24 and 60.

choosing the route of administration.[29] Non-adherence to psychotropic medication is one of the most important predictors for relapse, increasing risk fivefold in patients with first-episode schizophrenia and schizoaffective disorder and leading to relapse rate of more than 80% within 5 years.[30] There is increasing awareness that the early phases of psychosis represent a critical period for the treatment of schizophrenia and for its long-term prognosis.[31,32] Patients with first-episode schizophrenia initiated with antipsychotic therapy have sustained cognitive improvement for up to 2 years and this further encourages continuous, consistent, and stable plasma levels of antipsychotic therapy which can be achieved by prescribing LAI.[33] In those suffering from chronic schizophrenia, the availability of low frequency LAIs allows patients to focus on life goals, build self-confidence and limit stigma while minimising the risk of relapse.[34] When patients are fully informed and have tried LAI, they often view this route as preferable to oral, commenting that they 'feel better', have a more 'normal life' or find injections easier to remember and more convenient.[35,36]

In addition, treatment non-adherence has been found to be a predictor of violence risk.[37] Maintaining psychiatric treatment after release from prison can substantially reduce violent reoffending behaviour.[38] Naturalistic studies comparing oral to LAI in involuntary patients have revealed not only better adherence, fewer crisis and referrals in the LAI group,[39] but that LAI use may be an important tool to improve outcome in this cohort of patients.[40,41] Brissos and others have suggested a radical change in attitude among clinicians and patients, to reconsider LAI antipsychotics from a new perspective, not as a punitive route reserved for those with proven non-compliance after several trials with oral but a potential first step to ensure treatment is continued and to improve overall outcome.[5] The advantages OLAI gives towards medication compliance, relapse prevention, plasma level control and treatment outcome need to be balanced against perceived prejudices of LAI and management of relatively rare side effects such as PIS. Our study shows that with the right support, financially and logistically this route of administration can be sustained for many years in even the most unwell patients.

Table 5. Doses used throughout the study.

OLAI initial dose	Total (n = 88)
150 mg 2/52	13 (15%)
210 mg 2/52	43 (49%)
300 mg 10 days	1 (1%)
300 mg 2/52	23 (26%)
300 mg 4/52	2 (2%)
405 mg 10 days	1 (1%)
405 mg 2/52	4 (5%)
405 mg 4/52	1 (1%)
OLAI dose at 24 months for continuers	**Total (n = 45)**
150 mg 2/52	1 (2%)
210 mg 2/52	2 (4%)
300 mg 10 days	1 (2%)
300 mg 2/52	12 (27%)
300 mg 4/52	Nil
405 mg 10 days	17 (38%)
405 mg 2/52	9 (20%)
405 mg 4/52	3 (7%)

OLAI, olanzapine long-acting injection.

Strengths and limitations

This study has notable strengths; it is possibly the largest number of patients prescribed OLAI in a single setting in the United Kingdom. The hospital has robust digitalised documentation of prescriptions, monitoring for PIS, response and reasons for discontinuation. Overall, the ability of this unit to accommodate for the monitoring requirement for PIS did lead to a higher prescription rate and a lower dropout rate for our study.

This was an open, non-interventional study, with no control group, which is a potential limitation. Given the complexity of the Broadmoor hospital patient population, the number of service users on combination therapy, high doses of antipsychotic therapy, and previous use of clozapine make the outcomes appear less favourable in the first 24 months.

Adequate dosing to compare to usual practice is also difficult to interpret, as 60% of the patients who continued with OLAI were on higher than recommended doses by the manufacturer. Lack of olanzapine plasma levels for every service user makes it difficult to interpret the doses used and the ability of the service user to metabolise olanzapine.

Conclusion

OLAI is an effective treatment for schizophrenia and schizoaffective disorder, especially when used in patients who have been able to tolerate the drug and were stabilised on it for 24 months. In over half the patients who continued OLAI, the doses were higher than that recommended by the manufacturer. The incidence of PIS in this study was very low in comparison with the rate reported by the manufacturer and other studies.

Declarations

Ethics approval and consent to participate

This study was approved by the Broadmoor Medicines Management Committee as a service evaluation.

Consent for publication

Not applicable.

Author contribution(s)

Azizah Attard: Conceptualization; Data curation; Supervision; Writing – original draft; Writing – review & editing.

John Wakelam: Data curation; Investigation; Writing – review & editing.

Josephine Broyd: Data curation; Formal analysis; Software.

David Taylor: Supervision; Writing – review & editing.

Jonathan Hafferty: Methodology; Supervision; Writing – review & editing.

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research,

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Availability of data and materials

Not applicable.

ORCID iDs

Azizah Attard https://orcid.org/0000-0001-5590-4515

Josephine Broyd https://orcid.org/0000-0001-7377-2851

David Taylor https://orcid.org/0000-0002-2557-1710

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