Published in final edited form as:

Int Clin Psychopharmacol. 2017 May ; 32(3): 161–168. doi:10.1097/YIC.000000000000165.

Indications for and use of long-acting injectable antipsychotics: consideration from an inpatient setting

Taishiro Kishimoto^{a,b,c,i,*}, Sohag Sanghani^{a,b,*}, Mark J. Russ^d, Akeem N. Marsh^{a,e}, Joshua Morris^g, Suparna Basu^h, Majnu John^{a,c,f}, and John M. Kane^{a,b,c}

^aThe Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York

^bHofstra Northwell School of Medicine, Hempstead, New York

^cThe Feinstein Institute for Medical Research, Manhasset, New York

^dWeill Cornell Medical College New York-Presbyterian Hospital/Westchester Division, White Plains, New York

^eNew York University School of Medicine, New York, New York

^fDepartment of Mathematics, Hofstra, University, Hempstead, New York

^gEastside Medical Center, Snellville, Georgia

^hBaylor Scott and White Psychiatry, Irving, Texas, USA

ⁱDepartment of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

Abstract

Studies have examined the differences in sociodemographic/clinical characteristics between patients on long-acting injectable (LAI) versus oral medications. However, most studies did not focus specifically on patients for whom LAIs would clearly be indicated. We performed a chart review of patients with schizophrenia or schizoaffective disorder. Patients were categorized as having an ‘indication for an LAI’ or not on the basis of their adherence history. Patients for whom an LAI was indicated and prescribed on discharge were then compared with similar patients for whom an LAI was not prescribed. Of 305 charts reviewed, consisting of 279 unique patients,

Correspondence to Taishiro Kishimoto, MD, PhD, The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, NY 11004, USA, Tel: + 1 718 470 8386, fax: + 1 718 343 1659; taishiro-k@mti.biglobe.ne.jp.

*Taishiro Kishimoto and Sohag Sanghani contributed equally to the writing of this article.

T.K. contributed to designing the study, statistical analysis, and writing the report. M.R. contributed to designing the study, data extraction, and writing the report. S.S., A.M., J.M., and S.B. contributed to designing the study, data extraction, and writing the report. M.J. contributed to designing the study, statistical analysis, and writing the report. J.K. contributed to designing the study and writing the report.

Conflicts of interest

Dr. Kishimoto has received consultant fees from Daiippon Sumitomo, Novartis, and Otsuka, and speaker’s honoraria from Banyu, Eli Lilly, Daiippon Sumitomo, Janssen, Novartis, Otsuka, and Pfizer. He has received grant support from the Byoutaitaisyakenkyukai Fellowship (Fellowship of Astellas Foundation of Research on Metabolic Disorders) and the Eli Lilly Fellowship for Clinical Psychopharmacology.

Dr. Kane has been a consultant to Alkermes, Amgen, Astra-Zeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Daiippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Pierre Fabre, Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis, Roche, Rules Based Medicine, and Sunovion, and has received honoraria for lectures from Otsuka, Eli Lilly, Esai, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, and Janssen. He is a shareholder of MedAvante. He has received grant support from The National Institute of Mental Health. For the remaining authors there are no conflicts of interest.

27.2% were judged to have an indication for an LAI ($n = 76$), but only 32.9% of these ($n = 25$) were discharged on an LAI. In the multiregression model, being African American, residing in a psychiatric residence, having a previous history of an LAI trial, and being treated with a higher antipsychotic dose were predictive of LAI prescription. It is important to focus on the population who are not likely to receive an LAI, but who have such indications for treatment.

Keywords

antipsychotics; chart review; long-acting injectable; prescription; schizophrenia

Introduction

Nonadherence or poor adherence to taking medication is a universal problem in medical practice (Peterson *et al.*, 2003; DiMatteo, 2004; Osterberg and Blaschke, 2005). Nonadherence rates in patients with schizophrenia are known to be high in comparison with patients with other illnesses (Cramer and Rosenheck, 1998; Velligan *et al.*, 2009). Estimates in the literature range between 40 and 50%, but can be as high as 89% (Lacro *et al.*, 2002). Such high nonadherence rates in this population can limit the effectiveness of pharmacotherapy. Therefore, the use of long-acting injectable antipsychotics (LAIs) is considered to be an important treatment option (Kane and Garcia-Ribera, 2009; Barnes, 2011). Current guidelines recommend LAIs when adherence is inadequate (Lehman *et al.*, 2004; Canadian Psychiatric Association, 2005; Moore *et al.*, 2007; NCCMH, 2010). LAIs can not only ensure medication delivery among patients with poor adherence but also deal efficiently with covert nonadherence (Barnes and Curson, 1994), prevent abrupt loss of effectiveness if a dose is missed, relieve patients from the burden of daily dosing, and enable care providers to be immediately aware of nonadherence (Kane and Garcia-Ribera, 2009; Barnes, 2011). Moreover, it is reported that patients' attitudes toward LAIs are considerably more positive than is assumed by many clinicians (Wistedt, 1995; Pereira and Pinto, 1997; Walburn *et al.*, 2001; Waddell and Taylor, 2009; Caroli *et al.*, 2011).

Despite these advantages, LAIs are grossly underutilized (Fayek *et al.*, 2003). In the USA, the prescription rate in schizophrenia has never increased above 12% and has been estimated to be less than 6% in the most recent decade (Fayek *et al.*, 2003; Ahn *et al.*, 2008). Given the gap between the high nonadherence rate and the low LAI prescription rate, it is important to better understand the characteristics of patients who do and do not receive LAIs.

Factors related to LAI prescription have been studied previously. These include male sex, young age, an ethnic minority, more previous hospitalizations, living alone, more arrests in the past, alcohol and illicit substances use, nonadherence, previous use of an LAI, antipsychotic combination therapy, anticholinergic medication use, poor insight, more severe psychopathology, and disorganized thinking (Price *et al.*, 1985; Covell *et al.*, 2002; Kreyenbuhl *et al.*, 2003; Arnold *et al.*, 2004; Shi *et al.*, 2007; Vehof *et al.*, 2008; Aggarwal *et al.*, 2012). However, these reports are based on large prescription databases and generally compare patients on LAIs with patients on oral medications. Such data are not specifically focused on those patients for whom there are clear clinical indications for LAI use.

One major exception was a study carried out by West *et al.* (2008), which surveyed over 500 psychiatrists. LAI prescription was associated positively with the patient having public insurance, previous inpatient admission, the proportion of time the patient was nonadherent, average or above average intellectual functioning, and living in a mental health residence, whereas it was found to be inversely associated with using second-generation antipsychotics and other oral psychotropic medications (antidepressant, mood stabilizers and anxiolytics/hypnotics) before medication nonadherence. Another somewhat similar study from South Korea (Kim *et al.*, 2013) aimed to investigate the reasons for underuse of LAI and consisted of a survey of both psychiatrists and patients. Psychiatrists who were more familiar with LAI use were more likely to prescribe an LAI and their patients were more likely to have higher overall rates of satisfaction with the treatment compared with patient groups with psychiatrists who were less familiar with the treatment as they tended to recommend less and ultimately prescribe less. This is suggestive that there was a discrepancy between what some psychiatrists suspected in comparison with patients' actual beliefs about LAI treatment. Weaknesses of both studies include exclusive reliance on self-report and possible recall bias.

A better understanding of the pattern of LAI prescription may help to facilitate proper utilization in the future. We, therefore, examined consecutive (unselected) inpatient charts in which we established patients' history of adherence problems on the basis of their clinical record. This enabled us to explore the factors associated with LAI prescription among patients who had clear indications for LAI use.

Patients and methods

Materials

The study was carried out at The Zucker Hillside Hospital/Northwell Health, which is a 208-bed, private, not-for-profit psychiatric hospital located in a semiurban area of New York City and draws from a very large and diverse population. The electronic medical record system enabled us to select charts of consecutively admitted patients with specific diagnoses and review them electronically. We collected 400 charts of consecutive inpatient admissions with diagnoses of schizophrenia spectrum disorders, beginning 1 January 2010. As the aim of this study was to examine medical decision-making in terms of the utilization of LAIs, we excluded patients whose diagnoses were schizophreniform disorder, brief psychotic episode, psychotic disorder not otherwise specified, and whose primary diagnoses were nonschizophrenia spectrum. Moreover, although we acknowledge that the co-occurrence of developmental disability is one of the important characteristics of patients who are hospitalized multiple times, we excluded those patients, considering that the medical decision-making for such patients involves other factors. For similar reasons, we excluded patients with dementia. The study was approved by the Institutional Review Board of Northwell Health and was carried out in accordance with the ethical principles of the Declaration of Helsinki.

Chart review

Sociodemographic characteristics including age at the index hospitalization, sex, race/ethnicity, marital, domiciliary [whether patients live alone, with family, or in psychiatric residence (24-h staffed residences with supervised medication and skill training, apartments with staff visiting on regular and as needed basis, OR independent supported housing)], employment and insurance statuses, and criminal history were extracted from the charts. Diagnostic and therapeutic information including primary and secondary diagnoses, onset of illness, number of hospitalizations, medication history, alcohol use and illicit drug use in the preceding 3 months, lifetime drug abuse, duration of index hospitalization, and discharge medication was also extracted. Information on adherence was described on the basis of patients' and caregivers' reports. We stratified patients' adherence history into three categories: full adherence, meaning taking 100% or nearly 100% of the medication; non-adherence, meaning missing most of or all of the medication; and partial adherence, defined as intermediate between full and nonadherence, such that the patient missed a substantial proportion of the medication. Examples of the latter included taking doses on some, but not all days, receiving injections, but not taking prescribed oral medication concomitantly. Each hospitalization was categorized on the basis of these three adherence levels. We also attempted to determine the reasons for physician decision-making on the prescription of LAIs. Finally, with respect to postdischarge follow-up, we determined whether patients were readmitted within 3 months.

Indication for an long-acting injectable

None of the guidelines has clearly defined a recommended threshold for the initiation of LAIs. We therefore defined three such levels of indications to determine factors associated with LAI prescription. These three criteria are as follows:

1. Strong LAI indication: index hospitalization because of nonadherence AND at least two previous hospitalizations because of nonadherence.
2. Moderately strong LAI indication: index hospitalization because of nonadherence AND at least one previous hospitalization because of nonadherence.
3. Moderate LAI indication:
 - a. Index hospitalization because of nonadherence.
 - b. Partial-adherence before index hospitalization AND at least one previous hospitalization because of nonadherence.

We then calculated the proportion of admission cases that fulfilled these criteria and the proportion of admission cases that were discharged on LAIs to understand their utilization among patients for whom they are indicated with varying thresholds of rationale.

Sample size determination

The study sample was a convenience sample consisting of consecutively admitted inpatients with diagnoses of schizophrenia spectrum disorders, beginning 1 January 2010. As this was a descriptive, explorative study, we did not have a formal hypothesis to estimate the sample

size. Hence, we used the '10 cases (charts) per variable' rule, which has been used to determine the sample size in descriptive chart review studies (Harrell *et al.*, 1985; Findley and Daum, 1989; Sackett *et al.*, 1991; Gearing *et al.*, 2006).

We had 20 predictor variables in the final regression equation. According to the above rule, 200 charts would have been an adequate sample. To ensure that we were not compromising the power of the study as well as taking into account the possibility of identifying additional meaningful variables during the chart review, we decided to target around 300 charts to be included in the analysis. Given the possibility that we would have to exclude charts because of missing data and other reasons, we believed that 400 charts would be an adequate sample size.

Statistical analysis

Sociodemographic and diagnostic characteristics of the patients who met the LAI indication were compared with those of the patients who did not fulfill the criteria. To avoid analyzing patients who had multiple admissions during the study period, we excluded subsequent admission data from these analyses. For these comparisons, we chose level 2 criteria over level 1 or 3 (see Fig. 1 for definitions) as it is conservative and yet clearly shows an indication for using an LAI. Next, we compared patients with the level 2 criteria who were discharged on an LAI with those who were not. Distributions of all variables were inspected using histograms, q–q plots, and Shapiro–Wilks tests before carrying out statistical analyses. Differences in patient characteristics between groups were examined using χ^2 -analysis for categorical variables and analysis of variance or the Wilcoxon rank sum test for continuous variables. To determine the best predictive model for LAI prescription, we carried out a multivariate logistic regression analysis with stepwise backward elimination model selection method. Only the variables that were different between the two groups at a significance level of less than 0.1 in Table 1 were considered as potential predictors in the model selection method. All analyses were two sided, with α set at 0.05, using JMP 5.0.1, SAS V9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient demographics

A total of 400 charts starting from 1 January 2010 to 21 May 2010 were reviewed. Ninety-five charts were excluded from the analysis for the following reasons: comorbidity of developmental disability 44/95 (46.3%), likely primary diagnosis of mood disorder 22/95 (23.2%), likely primary diagnosis of psychotic disorder not otherwise specified 11/95 (11.6%), other principal diagnoses 15/95 (15.8%), and age younger than 18 years 3/95 (3.2%). A total of 305 charts were used for the analysis. Twenty patients were admitted two times, three patients were admitted three times, and one patient each was admitted four, five, and six times during the study period. Thus, a total of 279 unique patients contributed to the 305 admitted patients reviewed. Demographic characteristics of the 279 patients are shown in Table 1.

Adherence

The majority of charts provided information on adherence before the index hospitalization. Of 305 admissions, full adherence was reported in 87 (28.5%) instances of hospitalization. 58.4% of admissions were reported to have either nonadherence [125 (41.0%)] or partial adherence [53 (17.4%)]. Five patients were first episode (1.6%) and 35 (11.5%) admissions did not provide adequate adherence information.

Indication for long-acting injectables

Of 305 admissions, 50 (16.4%) cases had a strong indication for LAI administration (level 1), 84 (27.5%) cases had a moderately strong indication (level 2), and 156 (51.1%) cases had a moderate indication (level 3). In 55 (18.0%) of 305 admission cases, patients were prescribed LAIs (including an LAI and oral antipsychotic combination therapy). Patients' dispositions in each category are shown in Fig. 1. Among admission cases that fulfilled the criteria for LAI administration, 15/50 (30.0%), 28/84 (33.3%), and 42/156 (26.9%) were discharged on LAI for level 1, level 2, and level 3, respectively.

Reason for not prescribing a long-acting injectable

Reasons for not prescribing an LAI were rarely described in the chart. The reasons provided were previous failed trial [$n = 16$, adverse events ($n = 6$), poor adherence ($n = 3$), lack of effectiveness ($n = 1$), unknown ($n = 6$)], patient refusal ($n = 11$), patient on clozapine ($n = 5$), patient transferred to a long-term hospital ($n = 5$), and potential medical concern ($n = 2$). There were also two cases where LAI introduction was planned and oral formulation of the injection drug was started, but the LAIs were not initiated during the hospitalization.

Patient characteristics related to long-acting injectable indication and discharge on long-acting injectable

Differences in the demographic and diagnostic characteristics between patients who had clear indications for an LAI versus those who did not are shown in Table 1. Patients with indications for an LAI differed with respect to secondary diagnoses, were more likely to have substance/alcohol abuse or dependence, and have more frequent recent admissions compared with the patients without indications. We also found significant differences in race/ethnicity, residence, previous LAI trials, and chlorpromazine equivalent dose between patients who were discharged on an LAI and patients who were not discharged on an LAI despite indications (Table 1).

Predictor for long-acting injectable prescription

On constructing a stepwise backward elimination multiple regression model, prescription of LAI was significantly associated with being African American [odds ratio (OR): 12.4, 95% confidence interval (CI): 2.9–52.9, $P = 0.001$], living in psychiatric residence before admission (OR: 5.2, 95% CI: 1.4–20.0, $P = 0.016$), and higher chlorpromazine equivalent dose (OR: 1.002, 95% CI: 1.0003–1.0044, $P = 0.022$) ($r^2 = 0.503$, $P = 0.001$).

Readmission

Postdischarge data were available for 237 out of 305 admissions. Readmission within 3 months of discharge occurred in a total of 66 admission cases. Although patients discharged on LAI seemed less likely to be readmitted compared with patients not discharged on an LAI (19.5 vs. 29.6%), the difference did not reach statistical significance ($P = 0.19$).

Discussion

We performed a chart review to examine the impact of clinically determined and documented nonadherence on clinical practice and to explore factors associated with LAI prescription. Three major findings from the study should be emphasized.

First, we found that a large proportion of patients (58.4%) were admitted because of nonadherence or partial adherence to treatment. Moreover, many of these patients had a previous history of hospitalizations related to nonadherence. Because of the nature of the study, adherence information was extracted from what was written during the course of routine clinical assessment, that is, information was provided by patient and/or caregiver report. It is known that the prevalence of nonadherence increases when more precise assessment methods are applied, for example, blood levels of prescribed medication. It is likely, therefore, that the very high nonadherence and poor-adherence rate found in our study using retrospective methods biased by self-report is an underestimate of actual nonadherence rates. In addition, although LAIs have been shown to generally improve relapse prevention, recent research has shown that it is still possible with these agents despite adherence (Alphs *et al.*, 2016). Our results highlight the need for more detailed and accurate adherence assessment, especially when patients are experiencing relapse. An inaccurate assessment of adherence can lead psychiatrists to misinterpret patients' response or lack of response to medication. Physicians may increase the dose of medication because they believe that the current dose is not adequate for relapse prevention, when in fact the patient may actually not be taking the medication. Excessive doses of medication increase the risk of adverse effects, potentially contributing further toward nonadherence.

Second, LAIs were prescribed in only 1/4 to 1/3 of patients who had clear indications for LAIs on the basis of our definition. Although major guidelines recommend the use of LAIs when there is a risk of nonadherence (Lehman *et al.*, 2004; Moore *et al.*, 2007; Buchanan *et al.*, 2010; NCCMH, 2010), no guidelines specifically state under what circumstances LAIs should be used. We, therefore, defined three categories ('strong,' 'moderately strong', and 'moderate') for the LAI indication and examined the prescription rate in each category. It is likely that the low prescription rate in our population reflects the general trend of LAI use in the USA compared with the relatively high LAI utilization rate in some other countries, for example, 21.5% in Belgium (Hanssens *et al.*, 2006), 23.3% in New Zealand (Humberstone *et al.*, 2004), 25% in Australia (Castle *et al.*, 2002), 29% in the UK (Paton *et al.*, 2003), and 75.0% in Singapore (Sim *et al.*, 2004). Like Korea (Kim *et al.*, 2013), the prescription rate in the USA is very low (Fayek *et al.*, 2003). If the prescription rate of LAI is to increase, it is important to have a greater understanding of the underlying factors related to clinical utilization.

Third, when we compared patients for whom an LAI was indicated with those for whom it was not, the former were more likely to have substance/alcohol abuse or dependence and have more recent admissions. These findings are consistent with previous reports (Shi *et al.*, 2007). When we compared patients who were discharged on an LAI with those who were not despite having a clear indication, patients discharged on an LAI were more likely to be African American, living in a psychiatric residence, have previous LAI trials, and receive higher antipsychotic doses and were less likely to be White. Of these factors, African American race, living in psychiatric residence, and receiving a higher antipsychotic dose remained significant factors associated with LAI prescription in the multivariate regression analysis. In our clinical setting, we speculate that these factors may be further associated with the ethnic make-up of patients residing in our local psychiatric residences, the oversight of residences that may include the administration of LAIs, and a proxy for severity of illness, that is, use of high-dose antipsychotic strategies. The findings ultimately contribute toward our knowledge base with respect to which factors are associated with LAI prescription in clinical practice. We should also emphasize that those patients who did not have those characteristics were less likely to receive LAIs even though they might derive significant benefit from them. Psychiatrists may overlook the potential benefit of starting LAIs for such patients. In addition, there may be other factors that contribute toward the underprescribing of LAIs such as LAI availability on prescription drug formularies, cost, a facility's ability to administer, and patients' willingness to accept that we could not explore by means of chart review. Although we have identified several factors that were related to the prescription of LAIs in our cohort, it is also important to understand why the prescription rate is low in general. Previous research has suggested reasons for LAI underutilization listed as follows: the doctors' belief of increased adverse events (Kissling, 1994; Kane *et al.*, 1998), doctors' belief of negative attitudes of patients, stigma or negative image problem (Glazer and Kane, 1992; Heres *et al.*, 2006; Waddell and Taylor, 2009; Heres *et al.*, 2011), lack of prescribing knowledge and experience (Dencker and Axelsson, 1996), restrictive evidence (Kishimoto *et al.*, 2014), etc. Presumably, such factors combined with individual patient characteristics affect prescribers' decision-making. However, although such information about reasons for LAI underutilization is useful, it does not provide a clear picture of the direct/indirect factors involved in each decision-making process. To establish strategies to facilitate the appropriate use of LAIs in the future, we need to collect information from prescribers as to when and why they prescribe LAIs and why they do not, even when indicated on the basis of the actual patient's case.

The results of the study need to be interpreted in the context of several limitations. Because of the study design, the information was limited to the narrative data available in the medical records. With respect to obtaining information on the role of adherence before hospitalization, although we had relatively detailed information when the patients had been admitted to our hospital, it was not possible to obtain as accurate information in instances of hospitalization elsewhere. The lack of information on past admissions, however, is likely to have resulted in an underestimate of the true adherence rate. Therefore, one of our findings, that is, the low LAI prescription rate for patients who have indications for LAI treatment, was likely biased in a conservative direction. Another important limitation of our study is the lack of information on psychopathology. Factors such as poor insight likely influence the

decision to accept and prescribe LAIs. The proxy for the severity of psychopathology or relative treatment refractoriness in our analysis was chlorpromazine equivalent dose. We found that patients on higher doses were more likely to receive LAIs. However, the correlation of antipsychotic dose and the severity of psychopathology is unknown in our study. We could not adequately capture and study patients' admission legal status, legal status at the time of initiation of LAI, whether or not treatment was court ordered, and the relationship of these factors with the outcome of a patient receiving LAI. We found that in many charts, some fundamental information, for example, medication trial history such as dose, duration, response and adherence, or why/why not LAI was prescribed was not documented. Therefore, to make the best decisions for patients, this information is crucial and it is a significant impediment to optimal patient outcome. Documentation of detailed medication history should be a high priority for the field as a whole. Clinicians may want to consider regular administration of an adherence instrument such as the Brief Adherence Rating Scale. This scale is a pencil-and-paper, clinician-administered instrument used to assess adherence to oral antipsychotic medication in outpatients with schizophrenia and schizoaffective disorder. Results using this scale compare favorably to electronic monitoring (Byerly *et al.*, 2008).

Conclusion

We found that the majority of patients with schizophrenia and schizoaffective disorder admitted to our hospital had adherence-related problems. LAI prescription overall was underutilized when indicated on the basis of our criteria. Predictors for LAI prescription were African American race, living in a psychiatric residence, and higher dose of medication. It is important to focus on the patients who are less likely to receive an LAI as they may derive considerable benefit from them. Future studies need to collect information from prescribers as to when they prescribe LAIs and the reasons why they do not, even when indicated.

Acknowledgments

Funding for this study was supported in part by The Zucker Hillside Hospital Mental Advanced Center for Intervention and Services Research for the Study of Schizophrenia (MH090590) from the National Institute of Mental Health, Bethesda, Maryland, USA. The NIMH played no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Aggarwal NK, Rosenheck RA, Woods SW, Sernyak MJ. Race and long-acting antipsychotic prescription at a community mental health center: a retrospective chart review. *J Clin Psychiatry*. 2012; 73:513–517. [PubMed: 22579151]
- Alphs L, Nasrallah HA, Bossie CA, Fu D, Gopal S, Hough D, et al. Factors associated with relapse in schizophrenia despite adherence to long-acting injectable antipsychotic therapy. *Int Clin Psychopharmacol*. 2016; 31:202–209. [PubMed: 26974214]
- Ahn J, McCombs JS, Jung C, Croudace TJ, McDonnell D, Ascher-Svanum H, et al. Classifying patients by antipsychotic adherence patterns using latent class analysis: characteristics of nonadherent groups in the California Medicaid (Medi-Cal) program. *Value Health*. 2008; 11:48–56. [PubMed: 18237360]

- Arnold LM, Strakowski SM, Schwiers ML, Amicone J, Fleck DE, Corey KB, et al. Sex, ethnicity, and antipsychotic medication use in patients with psychosis. *Schizophr Res*. 2004; 66:169–175. [PubMed: 15061250]
- Barnes TR, Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2011; 25:567–620. [PubMed: 21292923]
- Barnes TR, Curson DA. Long-term depot antipsychotics. A risk-benefit assessment. *Drug Saf*. 1994; 10:464–479. [PubMed: 7917075]
- Barnes TR, Shingleton-Smith A, Paton C. Antipsychotic long-acting injections: prescribing practice in the UK. *Br J Psychiatry*. 2009; 52(Suppl):S37–S42.
- Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010; 36:71–93. [PubMed: 19955390]
- Byerly MJ, Nakonezny PA, Rush AJ. The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. *Schizophr Res*. 2008; 100:60–69. [PubMed: 18255269]
- Canadian Psychiatric Association. Clinical practice guidelines. Treatment of schizophrenia. *Can J Psychiatry*. 2005; 50(Suppl 1):7S–57S. [PubMed: 16529334]
- Caroli F, Raymondet P, Izard I, Plas J, Gall B, Delgado A. Opinions of French patients with schizophrenia regarding injectable medication. *Patient Prefer Adherence*. 2011; 5:165–171. [PubMed: 21573047]
- Castle D, Morgan V, Jablensky A. Antipsychotic use in Australia: the patients' perspective. *Aust N Z J Psychiatry*. 2002; 36:633–641. [PubMed: 12225447]
- Covell NH, Jackson CT, Evans AC, Essock SM. Antipsychotic prescribing practices in Connecticut's public mental health system: rates of changing medications and prescribing styles. *Schizophr Bull*. 2002; 28:17–29. [PubMed: 12047017]
- Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv*. 1998; 49:196–201. [PubMed: 9575004]
- Dencker SJ, Axelsson R. Optimising the use of depot antipsychotics. *CNS Drugs*. 1996; 6:367–381.
- DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care*. 2004; 42:200–209. [PubMed: 15076819]
- Fayek M, Flowers C, Signorelli D, Simpson G. Psychopharmacology: underuse of evidence-based treatments in psychiatry. *Psychiatr Serv*. 2003; 54:1453–1454. [PubMed: 14600298]
- Findley TW, Daum MC. Research in physical medicine and rehabilitation III: the chart review or how to use clinical data for exploratory retrospective studies. *Am J Phys Med Rehabil*. 1989; 68:150–157. [PubMed: 2730784]
- Gearing RE, Mian IA, Barber J, Ickowicz A. A methodology for conducting retrospective chart review research in child and adolescent psychiatry. *J Can Acad Child Adolesc Psychiatry*. 2006; 15:126–134. [PubMed: 18392182]
- Glazer WM, Kane JM. Depot neuroleptic therapy: an underutilized treatment option. *J Clin Psychiatry*. 1992; 53:426–433. [PubMed: 1362569]
- Hanssens L, De Hert M, Wampers M, Reginster JY, Peuskens J. Pharmacological treatment of ambulatory schizophrenic patients in Belgium. *Clin Pract Epidemiol Ment Health*. 2006; 2:11. [PubMed: 16734909]
- Harrell FE, Lee KL, Machar DB, Reichert TA. Regressive models for prognostic prediction: advantages, problems and suggested solutions. *Cancer Treat Rep*. 1985; 69:1071–1077. [PubMed: 4042087]
- Heres S, Hamann J, Kissling W, Leucht S. Attitudes of psychiatrists toward antipsychotic depot medication. *J Clin Psychiatry*. 2006; 67:1948–1953. [PubMed: 17194274]
- Heres S, Reichhart T, Hamann J, Mendel R, Leucht S, Kissling W. Psychiatrists' attitude to antipsychotic depot treatment in patients with first-episode schizophrenia. *Eur Psychiatry*. 2011; 26:297–301. [PubMed: 20570493]

- Humberstone V, Wheeler A, Lambert T. An audit of outpatient antipsychotic usage in the three health sectors of Auckland, New Zealand. *Aust N Z J Psychiatry*. 2004; 38:240–245. [PubMed: 15038803]
- Kane JM, Garcia-Ribera C. Clinical guideline recommendations for antipsychotic long-acting injections. *Br J Psychiatry*. 2009; 52(Suppl):S63–S67.
- Kane JM, Aguglia E, Altamura AC, Ayuso Gutierrez JL, Brunello N, Fleischhacker WW, et al. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. *Eur Neuropsychopharmacol*. 1998; 8:55–66. [PubMed: 9452941]
- Kim SW, Lee YH, Jang JE, Yoo T, Kim JM, Shin IS, et al. Comparison of attitudes toward long-acting injectable antipsychotics among psychiatrists and patients. *Int Clin Psychopharmacol*. 2013; 28:80–86. [PubMed: 23325306]
- Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014; 40:192–213. [PubMed: 23256986]
- Kissling W. Compliance, quality assurance and standards for relapse prevention in schizophrenia. *Acta Psychiatr Scand*. 1994; 382(Suppl):16–24.
- Kreyenbuhl J, Zito JM, Buchanan RW, Soeken KL, Lehman AF. Racial disparity in the pharmacological management of schizophrenia. *Schizophr Bull*. 2003; 29:183–193. [PubMed: 14552495]
- Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry*. 2002; 63:892–909. [PubMed: 12416599]
- Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004; 161(Suppl):1–56.
- Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, et al. The texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry*. 2007; 68:1751–1762. [PubMed: 18052569]
- NCCMH. Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care Updated edition. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists; 2010.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353:487–497. [PubMed: 16079372]
- Patel MX, David AS. Why aren't depot antipsychotics prescribed more often and what can be done about it? *Adv Psychiatr Treat*. 2005; 11:203–211.
- Paton C, Lelliott P, Harrington M, Okocha C, Sensky T, Duffett R. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. *J Psychopharmacol*. 2003; 17:223–229. [PubMed: 12870571]
- Pereira S, Pinto R. A survey of the attitudes of chronic psychiatric patients living in the community toward their medication. *Acta Psychiatr Scand*. 1997; 95:464–468. [PubMed: 9242840]
- Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm*. 2003; 60:657–665. [PubMed: 12701547]
- Price N, Glazer W, Morgenstern H. Demographic predictors of the use of injectable versus oral antipsychotic medications in outpatients. *Am J Psychiatry*. 1985; 142:1491–1492. [PubMed: 2866719]
- Sackett, DL., Haynes, RB., Guyatt, GH., Tugewll, P. Clinical epidemiology: a basic science for clinical medicine. Boston, MA: Little, Brown & Company; 1991.
- Shi L, Ascher-Svanum H, Zhu B, Faries D, Montgomery W, Marder SR. Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. *Psychiatr Serv*. 2007; 58:482–488. [PubMed: 17412849]
- Sim K, Su A, Ungvari GS, Fujii S, Yang SY, Chong MY, et al. Depot antipsychotic use in schizophrenia: an East Asian perspective. *Hum Psychopharmacol*. 2004; 19:103–109. [PubMed: 14994320]

- Taylor, D., Mir, S., Mace, S. Is cost a factor? A survey of psychiatrists and health authorities to determine the factors influencing the prescribing and funding of atypical antipsychotics. London: National Schizophrenia Fellowship; 1999.
- Vehof J, Postma MJ, Bruggeman R, De Jong-Van Den Berg LT, Van Den Berg PB, Stolk RP, et al. Predictors for starting depot administration of risperidone in chronic users of antipsychotics. *J Clin Psychopharmacol.* 2008; 28:625–630. [PubMed: 19011430]
- Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry.* 2009; 70(Suppl 4):1–48. [PubMed: 19686636]
- Waddell L, Taylor M. Attitudes of patients and mental health staff to antipsychotic long-acting injections: systematic review. *Br J Psychiatry.* 2009; 195(Suppl):S43–S50.
- Walburn J, Gray R, Gournay K, Quraishi S, David AS. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *Br J Psychiatry.* 2001; 179:300–307. [PubMed: 11581109]
- West JC, Marcus SC, Wilk J, Countis LM, Regier DA, Olfson M. Use of depot antipsychotic medications for medication nonadherence in schizophrenia. *Schizophr Bull.* 2008; 34:995–1001. [PubMed: 18093962]
- Wistedt B. How does the psychiatric patient feel about depot treatment, compulsion or help? *Nord J Psychiatry.* 1995; 49(Suppl 35):41–46.

Level 1: Strong LAI indication: Index hospitalization due to non-adherence AND ≥ 2 past hospitalization due to non-adherence
 Level 2: Moderately strong LAI indication: Index hospitalization due to non-adherence AND ≥ 1 past hospitalization due to non-adherence
 Level 3: Moderate LAI indication: 3-a) Index hospitalization due to non-adherence, OR 3-b) partial-adherence before index hospitalization AND ≥ 1 past hospitalization due to non-adherence
 Abbreviations: AP, antipsychotics; d/c, discharged; LAI, long acting injectable antipsychotics

Fig. 1.

Level 1: Strong LAI indication: Index hospitalization because of nonadherence AND at least two past hospitalization because of nonadherence. Level 2: Moderately strong LAI indication: Index hospitalization because of nonadherence AND at least one past hospitalization because of nonadherence Level 3: Moderate LAI indication: (a) Index hospitalization because of nonadherence, OR (b) partial adherence before index hospitalization AND at least one past hospitalization because of nonadherence. AP, antipsychotics; d/c, discharged; LAI, long-acting injection.

Table 1

Sociodemographic/diagnostic characteristics of patients with long-acting injection indication versus patients without indication, discharged on long-acting injection versus not discharged on long-acting injection

	All patients (<i>n</i> = 279)	All patients (<i>n</i> = 279)			Indication for LAI (<i>n</i> = 76)		
		No-indication for LAI (<i>n</i> = 203)	Indication for LAI (<i>n</i> = 76)	<i>P</i> -value	Discharged on LAI (<i>n</i> = 25)	Not Discharged on LAI (<i>n</i> = 51)	<i>P</i> -value
Male [<i>n</i> (%)]	174 (62.3)	123 (60.6)	51 (67.1)	0.32	18 (72.0)	33 (64.7)	0.52
Age [mean (SD)] (years)	42.1 (14.1)	42.9 (14.5)	39.8 (12.7)	0.11	36.0 (12.6)	41.7 (12.4)	0.06
Race/ethnicity [<i>n</i> (%)]				0.066			0.0022
African American	110 (40.4)	73 (37.1)	37 (48.7)	0.079 ^a	20 (80.0)	17 (33.3)	0.0001^a
White	96 (35.3)	73 (37.1)	23 (30.3)	0.29 ^a	2 (8.0)	21 (41.2)	0.0031^a
Hispanic	33 (12.1)	29 (14.7)	4 (5.3)	0.032^a	1 (4.0)	3 (5.9)	0.73 ^a
Asian	20 (7.4)	14 (7.1)	6 (7.9)	0.83 ^a	0 (0.0)	6 (11.8)	0.07 ^a
Others	13 (4.8)	7 (3.6)	6 (7.9)		2 (8.0)	4 (7.8)	
Single [<i>n</i> (%)]	222 (81.9)	159 (80.7)	63 (85.1)	0.39	22 (88.0)	41 (85.1)	0.62
Residence before admission				0.14			0.015
Home [<i>n</i> (%)]	165 (59.1)	122 (60.1)	43 (56.6)	0.59 ^a	11 (44.0)	32 (62.8)	0.12 ^a
Psychiatric residence [<i>n</i> (%)]	100 (35.8)	73 (36.0)	27 (35.5)	0.94 ^a	14 (56.0)	13 (25.5)	0.0090^a
Unemployed [<i>n</i> (%)]	253 (93.4)	183 (92.4)	70 (95.9)	0.30	24 (96.0)	46 (95.8)	0.97
Criminal history	48 (19.2)	41 (22.5)	7 (10.3)	0.029	2 (11.1)	11 (24.4)	0.23
Primary diagnosis [<i>n</i> (%)]				0.41			0.93
Schizophrenia	132 (47.3)	93 (45.8)	39 (51.3)		13 (52.0)	26 (51.0)	
Schizoaffective	147 (52.7)	110 (54.2)	37 (48.7)		12 (48.0)	25 (49.0)	
Secondary diagnosis [<i>n</i> (%)]				0.0046			0.60
None	212 (76.0)	158 (77.8)	54 (71.1)		18 (72.0)	36 (70.6)	
Substance abuse/dependence	43 (15.4)	23 (11.3)	20 (26.3)		7 (28.0)	13 (25.5)	
Obsessive compulsive disorder	6 (2.2)	6 (3.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Others	18 (6.5)	16	2		0 (0.0)	2 (3.9)	
Onset of illness				0.27			0.28
10 years ago	169 (70.7)	126 (73.7)	43 (63.2)		13 (56.5)	30 (66.7)	
5–9 years ago	30 (12.6)	19 (11.1)	11 (16.2)		6 (26.1)	5 (11.1)	

	All patients (<i>n</i> = 279)			Indication for LAI (<i>n</i> = 76)		
	All patients (<i>n</i> = 279)	No-indication for LAI (<i>n</i> = 203)	Indication for LAI (<i>n</i> = 76)	Discharged on LAI (<i>n</i> = 25)	Not Discharged on LAI (<i>n</i> = 51)	<i>P</i> -value
< 5 years ago	40 (16.7)	26 (15.2)	14 (20.6)	4 (17.4)	10 (22.2)	
Number of hospitalization in lifetime [mean (SD)]	6.2 (6.4)	5.9 (6.4)	6.9 (6.4)	6.4 (6.6)	7.2 (6.4)	0.24
Number of hospitalization in past 3 years [mean (SD)]	1.7 (1.9)	1.4 (1.8)	2.4 (2.1)	2.0 (2.5)	2.6 (1.9)	0.12
AP combination in the past	140 (69.0)	101 (69.2)	39 (68.4)	15 (83.3)	24 (61.5)	0.099
LAI trial in the past				19 (82.6)	16 (43.2)	0.0026
Alcohol use in last 3 months	41 (17.5)	21 (12.3)	20 (31.8)	6 (30.0)	14 (32.6)	0.84
Illicit drug use in last 3 months	56 (22.9)	33 (18.3)	23 (35.4)	9 (40.9)	14 (32.6)	0.51
Lifetime substance abuse	128 (53.1)	82 (47.4)	46 (67.7)	16 (72.7)	30 (65.2)	0.54
AP dose on discharge (CPZ equivalent) [mean (SD)] (mg/day)	540 (377)	563 (393)	476 (330)	673 (328)	383 (290)	< 0.0001
Length of stay [mean (SD)] (days)	35.7 (50.3)	35.1 (51.2)	37.5 (47.6)	35.2 (33.3)	38.6 (53.5)	0.31
Type of insurance						0.46
Medicare, Medicaid	216 (81.2)	150 (78.5)	29 (15.2)	21 (84.0)	45 (90.0)	
Commercial	37 (13.9)	66 (88.0)	8 (10.7)	4 (16.0)	4 (8.0)	

P < 0.05 are shown in bold.

Used level 2 definition (moderately strong indication for LAI = index nonadherence + 1 admission in the past because of nonadherence) for the analysis. AP, antipsychotics; CPZ, chlorpromazine; LAI, long-acting injection.

^aEach subgroup compared with all other subgroups combined, e.g. African-American versus non-African American (*P* = 0.079), White versus non-White (*P* = 0.29) etc.