

Effectiveness and Predictors of Continuation of Paliperidone Palmitate Long-Acting Injection Treatment

A 12-Month Naturalistic Cohort Study

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Abstract: Antipsychotic long-acting injectable (LAI) medication has an important place as a treatment option in schizophrenia with evolving evidence to support clinical benefit over oral medication. Paliperidone palmitate is recently licensed as an LAI. We studied a naturalistic cohort of all identifiable patients who initiated paliperidone LAI in a specific United Kingdom region (Sussex) from first availability up to January 2013 (n = 179). Favorably, 60% of the cohort continued paliperidone LAI beyond 12 months from initiation. Schizophrenia diagnosis was significantly associated with 12-month continuation on univariate analysis (65% continuation rate at 12 months in this diagnostic subgroup). No baseline variables were identified as independently associated with 12-month continuation. However, fewer inpatient days after initiation (odds ratio [OR], 1.01; 95% confidence interval [CI], 1.003–1.011; $P = 0.002$), dose adjustment up or down (OR, 3.46; 95% CI, 1.26–9.51; $P = 0.016$), and a higher maintenance dose (OR, 8.31; 95% CI, 1.84–37.51; $P = 0.006$) during treatment course were all independently associated with continuation on multivariate analysis. Our findings support the importance of a collaborative approach with the LAI recipient in treatment decision making to enhance treatment effectiveness.

Key Words: antipsychotic medications, schizophrenia, cohort study, paliperidone palmitate

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The efficacy of available long-acting injectable (LAI) antipsychotic medication in preventing relapse in schizophrenia has been clearly demonstrated in randomized studies versus placebo.^{1,2} The relative efficacy of LAIs versus oral medications, particularly of equivalent antipsychotic ligands, has been less easy to show, however. Meta-analysis of such LAI versus oral randomized studies over the last 15 years has increasingly demonstrated little measurable difference between the treatment modalities on relapse prevention.^{1,3,4} It is arguable, however, that patient samples included in such randomized studies are biased, for example, with potentially better treatment adherence and lower illness severity. Naturalistic studies may therefore provide important additional evidence to highlight any such differences and

provide clearer evidence for LAI effectiveness and their influence on longer-term illness outcome.

A recent systematic review of 25 naturalistic mirror-image studies, of at least 12 months' duration, found LAIs to be significantly superior to oral antipsychotics in preventing hospitalization for schizophrenia.⁵ Tiihonen et al⁶ investigated a large naturalistic cohort of patients with first episode psychosis in Finland, finding that risk of rehospitalization for patients receiving LAIs was approximately one third of that for those receiving oral medication (adjusted hazards ratio, 0.36; 95% confidence interval [CI], 0.17–0.75). Zhu et al⁷ explored all-cause discontinuation by 1 year for first-generation oral antipsychotics versus their equivalent LAI formulation in a naturalistic prospective sample of schizophrenia patients and reported that LAIs had a significantly longer time to discontinuation than oral medications.

Meta-analysis may enable comparison of intervention efficacy in larger combined samples of patients, and increasingly, the efficacy of commonly used antipsychotics (in non-treatment-resistant schizophrenia) seems to differ little between drugs.⁸ Individual patient factors that may influence treatment effectiveness are not reflected in such studies, however, and are equally as important to understand.

Over recent years, the availability of second-generation LAIs has broadened the therapeutic options for patients with schizophrenia. Paliperidone palmitate is a monthly antipsychotic injection indicated for the maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone, with licensed dose range from 25 to 150 mg. Recommended initiation of paliperidone palmitate is with 150 mg on treatment day 1 and 100 mg 1 week later (day 8), both administered in the deltoid muscle. Subsequent monthly maintenance injections can be within the dose range, although 75 mg is recommended.⁹

The aims of this study were to explore the clinical utility of paliperidone palmitate LAI in a large naturalistic sample by measuring 12-month discontinuation rate and to explore individual patient factors influencing discontinuation.

MATERIALS AND METHODS

Participants and Procedure

A naturalistic retrospective descriptive cohort study design was adopted to explore patients initiated on paliperidone palmitate LAI in Sussex, United Kingdom, from first availability until January 2013, in the publicly funded health service. Cases were identified through a register of all initiations in this region, held by the chief pharmacist. Data were collected on baseline demographics, diagnosis, previous treatment, reason for switch, setting on initiation and use of compulsory treatment (under the Mental Health Act), and treatment phase factors including compulsory treatment order use, dose change, inpatient bed use (all days added together over any admissions), and contact frequency with the prescriber. Duration of illness of more or less than 3 years was recorded

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as the earlier illness stage patients were managed by the early intervention service. The impact of these variables on discontinuation by 12 months was explored. To standardize across all patients (including those stopping without clinician input), time of discontinuation was recorded at the point that paliperidone palmitate LAI was not administered on its due date, rather than when the decision to discontinue was made. Data were entered by 1 investigator (R.F.) and subsequently validated by another (R.W.). Research governance and ethical approval were granted for this study by the locality research governance department.

Statistical Analysis

A 2-way contingency analysis (χ^2) was conducted to assess whether discontinuation at 12 months (yes vs no) had statistically different proportions in categorical variables, and a Student *t* test was performed to compare the groups in continuous variables. Univariate and multiple logistic regression analyses were conducted to identify baseline and treatment course variables associated with dichotomous 12-month discontinuation. Factors with a *P* value of less than 0.10 in the univariate analysis were included in the multivariate analysis.

RESULTS

Characteristics of the Study Sample

One hundred seventy-nine patients who initiated paliperidone palmitate in Sussex, United Kingdom, between July 2011 and January 2013, were identified. The cohort characteristics are presented in Table 1. The most common diagnosis was schizophrenia, although despite product licensing, 36% had other diagnoses. Most patients were being treated in the community at the time of initiation (61%). Reasons for switching to paliperidone palmitate LAI clustered into poor adherence to existing medication (60%) and switching from a less convenient/well-tolerated depot (40%). Most patients had previously been treated with 2 or more antipsychotics (92%), and 5 patients had previously been treated with clozapine. Reasons for not following the recommended initiation regime (in 17% of the cohort) were largely due to varying dose and timing of administration. The most commonly prescribed maintenance dose of paliperidone palmitate was 75 mg (in 40% of patients).

Six months after starting paliperidone palmitate, 73% (*n* = 131) were continuing this treatment, which decreased to 60% of the cohort (*n* = 108) by 12 months (as shown in Fig. 1). Of the 71 patients who discontinued treatment by 12 months, the main reasons clustered into "patient refused medication" (*n* = 43) and "poor clinical response" (*n* = 21). Other reasons included lost to follow-up (*n* = 2), planned discontinuation of antipsychotic with clinician (*n* = 2), deceased for reasons not related to treatment (*n* = 2), and poorly tolerated (*n* = 1). The mean time to discontinuation was 22.7 weeks in those who stopped within 12 months. The mean maintenance dose of paliperidone palmitate was significantly lower in the discontinued group (84.9 vs 103.0 mg for patients who were continuing treatment at 12 months; *P* < 0.001). Continuing LAI was significantly greater with a diagnosis of schizophrenia and not having a borderline personality disorder (*P* < 0.05 for both). Those switching from the combined group of oral risperidone or risperidone LAI (or both) similarly were significantly more likely to continue paliperidone LAI (*P* < 0.05). No patients switched from oral paliperidone. One hundred eleven patients (62%) were admitted to hospital at least once in the 12 months from LAI initiation, staying a mean of 105 total days across all admissions (range, 4–365 days; 10 cases remaining in hospital for 1 year from LAI initiation but 3 continuing LAI to this point). Those continuing treatment had

TABLE 1. Cohort Characteristics at Baseline, Treatment Phase Variables Over 12 Months From Initiation and 12-Month Continuation Rate of Paliperidone Palmitate LAI by Group

Variable	Total Cohort (<i>n</i> = 179)	Patients Continuing LAI (<i>n</i> = 108)
Age, mean (SD), range, y	40.5 (15), 19–76	41 (15), 19–76
Sex, male/female	115/64	75/33
Illness <3 y	51 (28)	30 (59)
Schizophrenia	115 (64)	76 (66)*
Schizoaffective disorder	20 (11)	12 (60)
Bipolar affective disorder	23 (13)	13 (57)
Other psychoses	11 (6)	5 (45)
Borderline personality disorder	10 (6)	2 (20)*
Inpatient initiation of LAI	70 (39)	41 (59)
Compulsory treatment at baseline	30 (17)	15 (50)
Clozapine use before LAI	5 (3)	3 (60)
Correct initiation as per SPC	149 (83)	89 (60)
Switched from oral medication	97 (54)	58 (60)
Switched from any depot	81 (45)	50 (62)
Switched from risperidone LAI	57 (32)	37 (65)
Switched from oral risperidone	45 (27)	28 (62)
Switched from risperidone oral/LAI	92 (54)	62 (67)*
Two or more previous antipsychotics	164 (92)	98 (60)
Medical reviews in 12 mo	2.3 (0–12)	2.3 (0–10)
Inpatient days in 12 mo	65.2 (0–365)	49.5 (0–365)*
Treatment order during 12 mo	13 (7)	5 (38)
Dose adjusted during 12 mo	47 (26)	39 (83) [†]
Maintenance dose, mg	95.8 (50–150)	103.0 (50–150) [†]

Unless indicated, total cohort data are presented as *n* (% of cohort) or mean (range). Among patients continuing LAI, data are presented as *n* (% of subgroup variable continuing LAI) or mean (range).

For comparison between dichotomous continuation at 12 months, χ^2 (categorical variables) or Student *t* test (continuous variables).

**P* < 0.05.

[†]*P* < 0.001.

SPC indicates summary of product characteristics.

significantly fewer inpatient days versus those discontinuing (mean 49.5 vs 89.0 days respectively, *P* = 0.014). Admission was not associated with paliperidone LAI discontinuation in all of those who were admitted while receiving it.

Analysis of Factors Associated With Treatment Continuation

The univariate analysis identified having a diagnosis of schizophrenia, not having a diagnosis of borderline personality disorder, the combined variable of switching from risperidone oral or LAI, having fewer inpatient days, dose adjustment (up or down), and a higher maintenance dose as significantly associated with treatment continuation at 12 months. The subsequent multivariate analysis identified fewer inpatient days, dose adjustment,

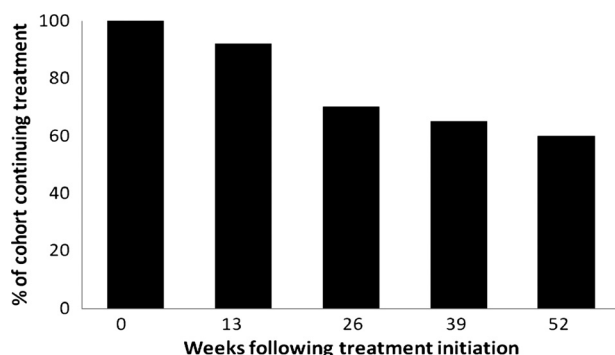


FIGURE 1. Percentage of patients continuing treatment with paliperidone palmitate LAI over 12 months' follow-up.

and a higher maintenance dose as significantly independently associated with continuation at 12 months (Table 2).

Subgroup Analysis of Patients With Schizophrenia

One hundred fifteen patients with a diagnosis of schizophrenia initiated paliperidone palmitate LAI, with a mean (SD) age of 41 (15) years (range, 19–71 years). Most patients were male (77%), and 63% were outpatients when initiated. The reasons

for switching to paliperidone palmitate LAI were poor adherence to existing medication (60%) and switching from a less convenient/well-tolerated depot (40%; 31% from risperidone LAI). Ninety-one percent had received at least 2 different antipsychotics previously, 4% had previously been prescribed clozapine, and only 32% were in their first 3 years from illness onset. The mean maintenance dose was 97.4 mg, with 75 mg being most frequently prescribed. Sixty-six percent of the patients were continuing treatment with paliperidone palmitate LAI at 12 months' follow-up. Of those who discontinued, the mean time to discontinuation was 22 weeks. Reasons for discontinuation were most prevalently patient refused treatment (27/39) and poor clinical response (9/39). Sixty-six patients (57%) had inpatient bed use in the 12 months after LAI initiation with a mean total admission days over this period of 110 days (range, 10–365 days; 6 cases remaining in hospital for 1 year from LAI initiation and only 1 continuing LAI to this point).

On multivariate analysis, variables independently associated with continuation at 12 months were dose adjustment during treatment (odds ratio [OR], 20.02; 95% CI, 2.03–197.82; $P = 0.010$), a higher maintenance dose (OR, 25.08; 95% CI, 1.57–400.13; $P = 0.023$), and fewer inpatient days (OR, 1.01; 95% CI, 1.00–1.02; $P = 0.003$). The only additional variable significant in the prior univariate analysis was not being under the Mental Health Act at initiation (OR, 0.27; 95% CI, 0.10–0.70; $P = 0.007$). Switch from

TABLE 2. Univariate and Multivariate Logistic Regression Analysis of Influence of Cohort Variables on Discontinuation of Paliperidone Palmitate LAI by 12 Months

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Age	0.99 (0.97–1.01)	0.196		
Sex, male vs female	1.76 (0.95–3.28)	0.075	1.20 (0.53–2.71)	0.669
Illness <3 y (no vs yes)	0.92 (0.47–1.77)	0.794		
Schizophrenia (no vs yes)	1.95 (1.04–3.64)	0.036	1.61 (0.71–3.63)	0.251
Schizoaffective disorder (no vs yes)	0.98 (0.38–2.54)	0.974		
Bipolar disorder (no vs yes)	0.84 (0.35–2.02)	0.689		
Other psychosis (no vs yes)	0.53 (0.15–1.79)	0.305		
Borderline PD (no vs yes)	0.23 (0.06–0.88)	0.032	0.16 (0.02–1.12)	0.065
Inpatient vs outpatient initiation	1.13 (0.61–2.08)	0.699		
Compulsory treatment at baseline (no vs yes)	0.60 (0.27–1.33)	0.207		
Prior clozapine use (no vs yes)	0.99 (0.16–6.05)	0.988		
Correct initiation as per SPC (no vs yes)	0.86 (0.38–1.93)	0.713		
Switched from oral medication (no vs yes)	0.95 (0.52–1.74)	0.872		
Switched from any depot (no vs yes)	1.11 (0.61–2.03)	0.729		
Switched from risperidone LAI (no vs yes)	1.33 (0.69–2.55)	0.393		
Switched from oral risperidone	1.14 (0.56–2.29)	0.723		
Switched from risperidone oral /LAI	1.96 (1.05–3.66)	0.034	1.85 (0.90–3.80)	0.092
2 or more previous antipsychotics (no vs yes)	0.74 (0.24–2.27)	0.602		
Medical reviews in 12 mo	1.03 (0.91–1.17)	0.605		
Inpatient days in 12 mo	1.004 (1.001–1.007)	0.012	1.01 (1.003–1.011)	0.002
Treatment order during 12 mo	0.38 (0.12–1.22)	0.104		
Dose adjusted during 12 mo (no vs yes)	4.52 (1.96–10.40)	<0.001	3.46 (1.26–9.51)	0.016
Maintenance dose		0.003		0.021
50 vs 150 mg	8.75 (1.94–39.57)	0.005	17.72 (2.71–115.99)	0.003
75 vs 150 mg	7.93 (2.53–24.82)	<0.001	8.06 (1.78–36.43)	0.007
100 vs 150 mg	4.66 (1.45–14.96)	0.010	8.31 (1.84–37.51)	0.006

Multivariate models include variables with $P < 0.10$ in the univariate analysis (in bold).

PD indicates personality disorder; SPC, summary of product characteristics.

risperidone oral or LAI was not a significant variable in this subgroup.

DISCUSSION

This large naturalistic cohort study demonstrates a relatively high rate of treatment continuation with paliperidone palmitate LAI, particularly in those with schizophrenia, and identifies treatment phase factors associated with continuation at 12 months. The nature of the cohort studied (with the majority being male, having illness established over several years, exposed to more than 2 previous antipsychotics, with poor antipsychotic adherence, and requiring significant amounts of hospitalization) gives insight into the clinical profiles of patient groups to which clinicians have offered this new LAI, although clinical reasoning is unclear. The 12-month all-cause discontinuation rate, often associated with treatment effectiveness,¹⁰ is therefore notably low and equivalent to that described by Attard et al¹¹ in a similar United Kingdom cohort exposed to paliperidone palmitate (with 65% continuing at 12 months). These discontinuation rates are markedly lower than the 6-month discontinuation rate for risperidone LAI of 53% reported in a similar clinical setting,¹² although conducted some years earlier. The clinical utility of paliperidone palmitate LAI is therefore supported by these findings, despite the use outside of its licensed indication (for the maintenance treatment of schizophrenia), and supports efficacy data.

We were surprisingly unable to show any impact of baseline factors on treatment continuation other than schizophrenia diagnosis, not having borderline personality disorder and switching from a similar medication (risperidone oral or LAI), none of these variables being independent factors. This supports antipsychotics not being recommended as primary treatment for borderline personality disorder.¹³ Numbers of those with markers of clear treatment resistance, such as previous clozapine use, were low, however. Attard et al¹¹ demonstrated a baseline association of 12-month paliperidone palmitate continuation with outpatient initiation, being switched from risperidone and correct initiation in accordance with the product's Summary of Product Characteristics,⁹ all *P* values less than 0.03 on multivariate analysis, in a similarly sized cohort. We concur with being switched from a similar medication (although only a trend to effect in our multivariate analysis), but the other factors are possibly more likely to influence early discontinuation. Being under the Mental Health Act at initiation significantly influenced discontinuation in the univariate analysis of the schizophrenia subsample; this may reflect lack of insight in the patient, which has a demonstrated association with poor treatment adherence,¹⁴ or reduced likelihood of collaborative treatment decision making with the clinician.

We demonstrate treatment phase factors independently associated with paliperidone palmitate continuation at 12 months of a higher maintenance dose, having fewer inpatient days and dose adjustment (up or down). It is possible that a higher dose is more likely with a longer period of drug exposure, particularly in a group with advanced illness, although we did not observe mean paliperidone dose increasing over time in this cohort. A greater dose in the continuing group may imply greater effectiveness in the higher recommended dose range, which is not clearly evident from earlier short-term efficacy studies.¹⁵ Although adverse effects would be expected to be greater in higher doses, these are not consistently associated with treatment discontinuation.¹⁶ Inpatient stays may be associated with a greater likelihood of different treatment trials and earlier discontinuation than outpatient status (particularly with a low yearly mean number of outpatient clinician reviews) or simply the result of paliperidone LAI not having efficacy in some individuals. Inpatient clinicians are likely to be

more sensitive to changes in positive symptoms than functional recovery, which is more demonstrable as outpatients over a longer period. Inpatient bed days may also be the most sensitive indicator of illness severity in our sample. Dose adjustment as an independently significant variable may indicate the importance of collaborative treatment decision making, although a hypothesized association of continuation with number of medical reviews was not demonstrated (contact frequency with key worker was not recorded). This argument is consistent with an observed trend to treatment discontinuation in those exposed to a community treatment order during the 12 months' follow-up, implying less collaborative illness management, although numbers were low. An evidence base of more collaborative treatment attitudes improving treatment effectiveness and longer-term illness outcome is evolving.^{17,18}

This is a naturalistic retrospective study designed to investigate clinical variable associations with real-world effectiveness outcomes via within-sample analysis; we acknowledge the inherent limitations of such a study, particularly the lack of a direct comparator and randomization. Variables chosen were within governance approval boundaries and likely to be robustly recorded. Time to discontinuation was measured at a point which may be longer than when the decision to discontinue was made, but the time point chosen was deemed the most accurate across all reasons for discontinuation and individuals were likely to have active medication effect until at least this time point. Exploring the complexity of reasons for discontinuation would require more detailed prospective qualitative methodology. The impact of using LAI preparations in a less morbid sample and at an earlier treatment stage, as supported by patient preference surveys,¹⁹ would also be valuably studied. Data on concurrent medications and other medical conditions in this cohort were complex and inconsistently available, so their effect on discontinuation was unable to be assessed; better systematic recording in a prospective study would be important to more clearly explore their influence.

In conclusion, variables influencing 12-month LAI continuation may notably reflect collaborative treatment decision making with the LAI recipient and dose adjustment to improve effect and tolerability. The clinical utility of paliperidone palmitate LAI is supported.

AUTHOR DISCLOSURE INFORMATION

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REFERENCES

1. Adams CE, Fenton MK, Quraishi S, et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry*. 2001;179:290–299.
2. Hough D, Gopal S, Vijapurkar U, et al. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res*. 2010;116:107–117.
3. Leucht C, Heres S, Kane JM, et al. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. *Schizophr Res*. 2011;127:83–92.
4. Kishimoto T, Robenzadeh A, Leucht C, 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.
5. Kishimoto T, Nitta M, Borenstein M, et al. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry*. 2013;74:957–965.

6. Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168:603–609.
7. Zhu B, Ascher-Svanum H, Shi L, et al. Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia. *Psychiatr Serv*. 2008;59:315–317.
8. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382:951–962.
9. Summary of product characteristics. XEPLION prolonged release suspension for injection. December 16, 2013. Available at: <http://www.medicines.org.uk/emc/medicine/24403>. Accessed January 13, 2015.
10. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.
11. Attard A, Olofinjana O, Cornelius V, et al. Paliperidone palmitate long-acting injection—prospective year-long follow-up of use in clinical practice. *Acta Psychiatr Scand*. 2014;130:46–51.
12. Taylor DM, Young C, Patel MX. Prospective 6-month follow-up of patients prescribed risperidone long-acting injection: factors predicting favourable outcome. *Int J Neuropsychopharmacol*. 2006;9:685–694.
13. National Institute for Health and Clinical Excellence. *Borderline personality disorder: treatment and management*. NICE clinical guideline CG78. Manchester: NICE; 2009. Available at: www.nice.org.uk/guidance/cg78. Accessed January 13, 2015.
14. Baloush-Kleinman V, Levine SZ, Roe D, et al. Adherence to antipsychotic drug treatment in early-episode schizophrenia: a six-month naturalistic follow-up study. *Schizophr Res*. 2011;130:176–181.
15. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacol*. 2010;30:235–244.
16. Kikkert MJ, Schene AH, Koeter MW, et al. Medication adherence in schizophrenia: exploring patients', carers' and professionals' views. *Schizophr Bull*. 2006;32:786–794.
17. Wunderink L, Nieboer RM, Wiersma D, et al. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*. 2013;70:913–920.
18. The Schizophrenia Commission. *The Abandoned Illness: A Report From the Schizophrenia Commission*. London: Rethink Mental Illness; 2012. Available at: www.rethink.org. Accessed January 13, 2015.
19. Caroli F, Raymondet P, Izard I, et al. Opinions of French patients with schizophrenia regarding injectable medication. *Patient Prefer Adherence*. 2011;5:165–171.