

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/87141/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Deslandes, Paul, Dwivedi, Matthew and Sewell, Robert David Edmund 2015. Five-year patient outcomes with risperidone long-acting injection or oral aripiprazole. *Therapeutic Advances in Psychopharmacology* 5 (3) , pp. 151-157.
10.1177/2045125315581997

Publishers page: <http://dx.doi.org/10.1177/2045125315581997>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



**Five year patient outcomes with risperidone long-acting injection or oral
aripiprazole**

(Running title: Five year patient outcomes with antipsychotic treatment)

by

Paul N. Deslandes^{1,2}, Matthew Dwivedi¹, Robert D.E. Sewell¹

¹Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff,
CF10 3NB. ²Pharmacy Department, Whitchurch Hospital, Park Road, Cardiff, CF14 7XB.

Author for correspondence:

Dr Paul N. Deslandes

Pharmacy Department

Whitchurch Hospital

Park Road

Cardiff

CF14 7XB

UK

Tel: +44(0)2920 336535

Fax +44(0)2920 336350

Email: paul.deslandes@wales.nhs.uk

Abstract:

Objectives: This study examined five year outcomes of patients prescribed risperidone long-acting injection (RLAI) or aripiprazole in a clinical setting, using treatment discontinuation as a measure of effectiveness.

Method: Patients who received RLAI or aripiprazole in the 18 months following their respective UK launches were included. Two year outcome data has previously been reported for these cohorts; this study reported an additional three years of follow-up for each group. Data were collected from pharmacy records and by retrospective case note review. Patients were classified as continuers or discontinuers at five years, and reasons for treatment discontinuation noted.

Results: The number of patients remaining on treatment at two years (and included in this study) was 28/84 and 27/92 for RLAI and aripiprazole respectively. Of the 55 patients included, two treated with RLAI and three treated with aripiprazole were lost to follow-up. Therefore, five year outcome data were available for 50 patients (26 RLAI and 24 aripiprazole). Fifteen patients from each group were continuers at five years. Of the 30 continuers, four receiving RLAI and three receiving aripiprazole were co-prescribed other antipsychotics at study endpoint. Reasons for discontinuation of RLAI and aripiprazole respectively were a lack of effect (n=4; 4), adverse effects (n=3; 1), non-compliance or patient choice (n=2; 4), and patient death (n=2; 0).

Conclusions: There was no significant difference between the proportions of patients continuing RLAI or aripiprazole for five years. Continuation rates were relatively low (18% and 16% of the original RLAI and aripiprazole cohorts respectively), whilst co-prescription of other antipsychotics at endpoint was relatively common. Lack of effectiveness was the most common reason for discontinuation of both compounds. These findings suggested that clinical effectiveness was somewhat disappointing although the long period of follow-up and number of patients previously treated with clozapine in the original cohorts were confounding factors.

Keywords: antipsychotic agents/therapeutic use; risperidone, aripiprazole

Introduction:

The antipsychotic treatments risperidone long acting injection (RLAI) and aripiprazole (tablet formulation) have been available in the UK since October 2002 and July 2004 respectively. When launched, both represented novel approaches to the treatment of psychosis. RLAI was the first available long acting injectable preparation of an atypical antipsychotic, with the potential advantages of reduced covert non-adherence compared to oral medication (Barnes and Curson, 1994) and reduced propensity for extra-pyramidal side effects compared with typical antipsychotics (Leucht et al., 1999). Aripiprazole had a novel pharmacology, (with partial agonist rather than antagonist properties at the dopamine D2 receptor) which suggested that it would be associated with a favourable adverse effect profile (Taylor, 2003) together with the potential associated benefits of improved adherence and outcome (Lambert and Naber, 2004).

Data from randomised controlled trials (RCTs) have provided evidence for the efficacy of RLAI (Kane et al., 2003) and aripiprazole (Potkin et al., 2003) in the treatment of psychosis. However, RCTs typically assess treatment outcome over a short period of time, which may have limited applicability to the clinical management of a chronic illness such as schizophrenia. Furthermore, due to strict inclusion and exclusion criteria, participants may not be representative of patients routinely seen in practice. Consequently, naturalistic patient follow-up studies (e.g. Attard et al., 2014), and studies using pragmatic outcome measures (e.g. Lieberman et al., 2005) have been used to evaluate the effectiveness of a number of different antipsychotics in settings more relevant to clinical practice. Both RLAI and aripiprazole have been the focus of several such studies with periods of follow-up ranging from six months (Deslandes et al., 2008; Taylor et al., 2007) to three years (Taylor et al., 2009). Given the chronic and relapsing nature of schizophrenia and the burden of the disease, studies with longer periods of follow-up remain important to assess treatment outcome (Turner, 2004).

This study examined five year outcomes of patients prescribed RLAI or oral aripiprazole in a clinical setting, using treatment continuation as a measure of effectiveness in order to evaluate their longer term value.

Methods:

Design

This was a retrospective, naturalistic follow-up study of patients with a diagnosis of schizophrenia or schizoaffective disorder, prescribed RLAI or aripiprazole tablets in clinical practice in the two years following their respective UK introductions. Two year outcome data has previously been reported for these cohorts (Deslandes et al., 2009a and 2009b). This study reported an additional three years of follow-up for patients continuing either treatment at two years. The original study was reviewed by the South East Wales Research Ethics committee panel C (reference number 04/WSE03/25).

Participants and outcome measures

Out of the original cohorts of 176 patients (84 RLAI and 92 aripiprazole), those remaining on treatment at two years were identified. Data were collected from pharmacy records and by retrospective case note review during a six week period throughout February and March 2013. Patients were retrospectively categorized either as those remaining on treatment (at five years), classified as “continuers”, or individuals who had discontinued treatment and designated “discontinuers”. The reason for discontinuation was recorded for all patients who stopped treatment during the study period. Where the reason for discontinuation was recorded as “patient refusal”, subjects were either disengaging from mental health services, or exhibited a lack of insight resulting in them refusing treatment. In some cases, adverse effects were the primary reason for a patient refusing (and discontinuing) treatment, such individuals were categorised as discontinuing due to adverse effects. The duration of treatment and the antipsychotic to which patients were switched following discontinuation were also noted. Patients’ drug histories were reviewed in order to determine whether or not they had previously been treated with

clozapine. This information was used to provide an indication that their condition had previously been unresponsive to treatment. Due to a possible association between RLAI discontinuation in patients who had previously experienced two treatment failures with other antipsychotics (Deslandes et al., 2009a), this information was also recorded. For patients prescribed aripiprazole, inpatient or outpatient status at initiation was recorded. The maintenance dose upon treatment discontinuation (or at five years for continuers) and the details of any co-prescribed antipsychotics were recorded for all patients.

Analysis

Outcomes of patient subgroups based upon previous clozapine treatment, two or more previous treatment failures and inpatient versus outpatient status at initiation were compared. Continuous variables were compared using unpaired Student t-test. Chi-squared test or Fisher's Exact test were used to compare categorical data. All statistical analyses were conducted using InStat (Instant Biostatistics) version 3.0 (GraphPad Software, USA).\

Results:

The number of patients remaining on treatment at two years (and therefore included in this study) was 28/84 and 27/92 of the original RLAI and aripiprazole cohorts respectively. Out of the 55 patients included, two treated with RLAI and three treated with aripiprazole were lost to follow-up. Therefore, five year outcome data were available for 50 patients (26 RLAI and 24 aripiprazole). Six patients receiving RLAI and seven receiving aripiprazole had previously been treated with clozapine. Patient demographics, reasons for treatment initiation and mean dose at study endpoint are shown in table 1.

Table 1. Patient demographics and reasons for treatment initiation

	RLAI		Aripiprazole	
	Continuers (n=15)	Discontinuers (n=11)	Continuers (n=15)	Discontinuers (n=9)
Age at initiation (years)				
Mean \pm sd	37.5 \pm 9.2	38.5 \pm 17.3	40.5 \pm 12.8	44.7 \pm 12.7
Range	20–53	19–70	19–71	33–71
Gender n (%)				
Male	10 (67)	8 (73)	7 (47)	3 (33)
Female	5 (33)	3 (27)	8 (53)	6 (67)
Ethnicity n (%)				
Caucasian	15 (100)	6 (55)	11 (73)	9 (100)
Non-caucasian	0 (0)	5 (45)	4 (27)	0 (0)
Previous clozapine n (%)	4 (27)	2 (18)	2 (13)	5 (56)
Two or more previous antipsychotic trials n (%)	4 (27)	2 (18)	11 (73)	9 (100)
Status on initiation n (%):				
Inpatient	–	–	2 (13)	4 (44)
Outpatient	–	–	13 (87)	5 (56)
Reason for initiation n (%)				
Previous non-compliance	14 (93)	11 (100)	0 (0)	2 (22)
Previous poor response	1 (7)	0 (0)	5 (33)	4 (44)
Previous adverse effects	0 (0)	0 (0)	9 (60)	3 (33)
Patient choice	0 (0)	0 (0)	1 (7)	0 (0)

Patients continuing treatment:

The proportion of patients remaining on treatment over time is shown in figures 1 and 2. Figure 1 shows the proportion of the original RLAI and aripiprazole cohorts on treatment from time 0 to five years excluding those lost to follow-up in the current study (n=82 and n=89 for RLAI and aripiprazole respectively). Figure 2 shows the proportion of continuers at year two (n=50) remaining on treatment from year two up to the study endpoint at year five according to whether they had previously been treated with clozapine (C) or had not previously been treated with clozapine (NC). Fifteen patients from each cohort were continuers at five years; there was no significant difference between the proportions continuing RLAI or aripiprazole (p=0.73 Chi-square test). Previous clozapine treatment or a history of two or more previous treatment failures did not predict outcome with either RLAI (p=1.0 Fisher's Exact test) or aripiprazole (p=0.06 and 0.26 respectively, Fisher's Exact test). Similarly inpatient or outpatient status at initiation did not predict aripiprazole outcome (p=0.15 Fisher's Exact test). Mean doses \pm sd at five years were 47.5mg \pm 15.8mg and 16.8mg \pm 8.4mg for RLAI and aripiprazole respectively. Four of the RLAI continuers (26%) and one of the aripiprazole continuers (7%) were co-prescribed other antipsychotics at five years. Risperidone (n=3) and amisulpride (n=1) were the co-prescribed antipsychotics in the RLAI cohort, and chlorpromazine was the co-prescribed antipsychotic in the aripiprazole cohort.

Five year patient outcomes with antipsychotic treatment

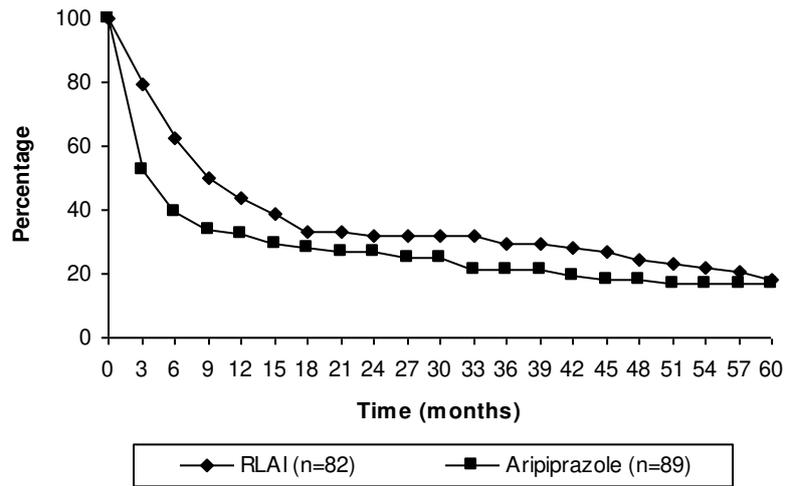


Figure 1. Proportion of original patient cohorts remaining on treatment over time

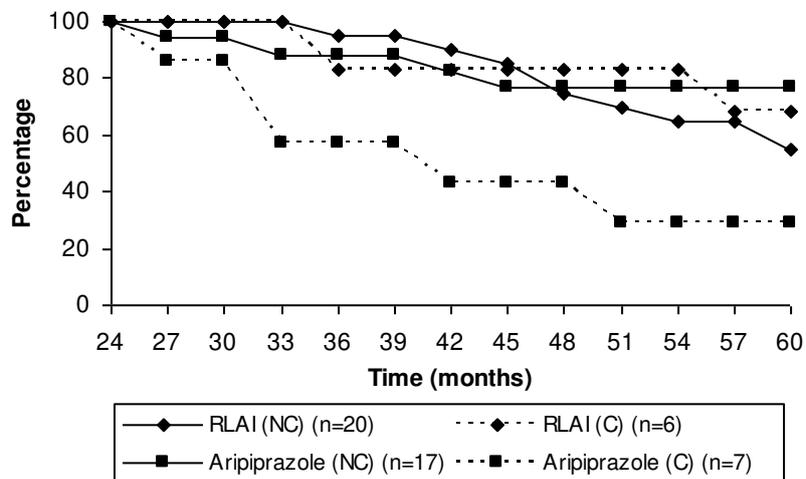


Figure 2. Proportion of patients remaining on treatment from 2–5 years

Patients discontinuing treatment:

Reasons for treatment discontinuation, dose at discontinuation and the antipsychotic to which patients were switched are shown in table 2. Patients were categorized by treatment and according to whether or not they had previously received clozapine. Doses for the RLAI group represent mean fortnightly dose. Poor response was the most common reason for discontinuation in both groups.

Table 2 Reasons for discontinuation

	RLAI		Aripiprazole	
	Clozapine (n=2)	Non-clozapine (n=9)	Clozapine (n=5)	Non-clozapine (n=4)
Dose at discontinuation (mg)				
Mean \pm sd	50 \pm 0	38.4 \pm 17.5	24.0 \pm 8.2	15 \pm 10
Range	50	25–75	15–30	10–30
Reason for discontinuation. (n)				
Poor response	2	2	3	1
Non-compliance	0	1	1	2
Adverse effects	0	3	1	0
Patient choice	0	1	0	1
Patient death	0	2	0	0
Switched to. (n)				
Oral atypical (not clozapine)	0	7	2	2
Oral typical	0	0	2	0
Long acting atypical	0	0	1	0
Clozapine	2	0	0	0
No treatment	0	2	0	2

Discussion:

This study assessed clinical outcomes of patients treated with two novel antipsychotic preparations over an extended period of time. Overall continuation rates from time 0 to five years for the original cohorts of 176 patients were relatively low (18% and 16% of RLAI and aripiprazole treated patients respectively). However, of the 50 patients remaining on treatment at two years (the focus of the present study), 60% completed an additional three years of treatment, and were therefore continuers at five years. There was no significant difference between the proportions of patients continuing RLAI or

aripiprazole at five years. Reasons for discontinuation were comparable, with lack of effectiveness being the most common reason for cessation of both compounds. Co-prescription of other antipsychotics was relatively common (17% of all continuers at five years).

This study was not specifically designed to compare outcomes between patients treated with either RLAI or oral aripiprazole or between subgroups of patients treated with each drug. Indeed, data from the two cohorts were collected over different time periods and the demographics of the two groups (particularly reasons for treatment initiation) were different. However, there was no significant difference in the proportion of patients continuing either drug at five years, although it must also be noted that there may not have been sufficient power to detect such a difference. This is consistent with the findings of a two year, open label study examining outcomes with these antipsychotics (Macfadden et al., 2010). It has been suggested that long-acting injectable formulations of antipsychotics may be more effective than oral formulations of the same drug (Tihonen et al., 2006). This may be due to a reduction in overt non-compliance associated with the long-acting injections, with subsequent benefits in treatment outcome (Novick et al., 2010). Whilst overall levels of discontinuation in our study were similar, it is perhaps interesting to note that the proportion of patients discontinuing due to non-compliance (9% and 33% for RLAI and aripiprazole respectively) favoured the long-acting injectable preparation in this regard. Conversely, the proportion of patients discontinuing due to adverse effects (27% and 11% for RLAI and aripiprazole respectively) suggested that the hypothesized improved tolerability profile of aripiprazole (Taylor, 2003) has been realised in clinical practice. It should be noted that in addition to the limitations mentioned above, the number of patients discontinuing due to these reasons was small (n=8) making it difficult to draw definitive conclusions from these findings.

The proportion of patients discontinuing treatment, and the level of antipsychotic co-prescribing at five years suggested that the clinical effectiveness of both RLAI and

aripiprazole was somewhat disappointing. However, the long period of follow-up and large number of patients previously treated with clozapine in the original cohorts were confounding factors. Results with RLAI at three years (29% continuation) were consistent with the findings of another naturalistic study, which reported a 33% continuation rate at the same time point (Taylor et al., 2009). An open label study comparing RLAI and aripiprazole over two years reported continuation rates of 69% and 61% respectively, with 7.9% of RLAI and 11% of aripiprazole patients co-prescribed an antipsychotic (Macfadden et al, 2010). The continuation rate was somewhat higher than that seen in our study at two years, which may reflect the differing study designs. At five years, 26% of RLAI and 7% of aripiprazole continuers in our study were co-prescribed an antipsychotic. The rate of co-prescribing with aripiprazole was comparable to that seen by Macfadden et al., (2010). The rate for RLAI was considerably higher, although somewhat lower than the 46% reported by Aggarwal et al (2012) in a study of antipsychotic long-acting injection use in clinical practice in the USA. The five year follow-up period in the present study may explain this difference, as patients requiring supplementation (and therefore presumably showing a sub-optimal response to treatment) may have discontinued prior to study end-point. Oral risperidone was the most commonly co-prescribed medicine in the RLAI group. This perhaps suggested that patients showed some response but required a higher plasma level of the drug than that provided by the injectable formulation alone in order to achieve a maximal response.

Whilst discontinuation over the whole five year period was high, continuation of treatment at year two appeared to be a relatively good predictor of continuation at year five for both of the treatments studied. Findings from the RLAI cohort showed that previous poor response to antipsychotic treatment was associated with early discontinuation (Deslandes et al., 2009). It could be argued that excluding patients who discontinued early (< 1 year) in treatment, and assessing response over the subsequent four years would have shown a more positive outcome. This is consistent with the view that in clinical practice newly launched antipsychotics are often prescribed for hard to treat

patients who have failed to respond to other drugs, thereby increasing the likelihood of treatment failure (Young and Taylor 2006). However, it should also be noted that longer term studies indicate that patients with schizophrenia tend to stabilise in any event after approximately five years through the natural alleviations of the disease and with progressing age and maturity (Harrison et al., 2001). Despite all of the patients who discontinued RLAI being initiated due to poor compliance, the agent that they were switched to following discontinuation was an oral (non-clozapine) atypical antipsychotic. This would appear somewhat illogical if previous poor compliance had been a reason for initiation of long-acting injectable treatment. Subsequent outcomes for this subgroup were not evaluated, but would be of potential benefit in order to explore the effectiveness of this treatment approach.

This study provided evidence for the effectiveness of RLAI and aripiprazole in a real-world clinical setting over an extended time period. Continuation rates with both compounds over the whole five year period were somewhat disappointing which may have been due in part to the long period of follow up and number of patients previously treated with clozapine. However, a relatively large proportion of the two cohorts included in the present study remained on treatment from year two to year five, which highlighted the importance of appropriate prescribing to minimize early discontinuation and achieve good outcomes in a clinical setting.

Sources of funding: This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements: The authors thank Mrs W. Davies for the opportunity to conduct this work.

Declarations of conflicting interest: PND has received payment for presentations and funding to attend scientific meetings from Janssen-Cilag Ltd, and payment to attend advisory board meetings from Schering-Plough.

References:

- Aggarwal NK, Sernyak NJ, Rosenheck RA. (2012) Prevalence of concomitant oral antipsychotic drug use among patients treated with long-acting, intramuscular, antipsychotic medications. *J Clin Psychopharmacol* 32: 323-328
- Attard A, Olofinjana O, Cornelius V, Curtis V, Taylor D. (2014) Paliperidone palmitate long-acting injection – prospective year-long follow-up of use in clinical practice. *Acta Psychiatr Scand* 130: 46-51
- Barnes TRE, Curson DA. (1994) Long-acting depot antipsychotics: a risk–benefit assessment. *Drug Safety* 10: 464-479
- Deslandes PN, Thomas A, Blackmore EE, Sewell RDE. (2008) Aripiprazole: 6-month outcomes in a retrospective naturalistic study. *Int J Psych Clin Prac* 12: 243-246
- Deslandes PN, Thomas A, Lewis A, Sewell RDE. (2009a) Risperidone Long Acting Injection: Findings of a two year retrospective follow-up study. *Int J Psych Clin Prac* 13: 298-302
- Deslandes PN, Khir A, Sewell RDE. (2009b) Aripiprazole: two year outcomes in a retrospective naturalistic study *J Psychopharmacol* 24 (suppl 3): A14
- Harrison G, Hopper K, Craig T, Laska E, Siegel C, Wanderling J, Dube KC, Ganey K, Giel R, an der Heiden W, Holmberg SK, Janca A, Lee PW, León CA, Malhotra S, Marsella AJ, Nakane Y, Sartorius N, Shen Y, Skoda C, Thara R, Tsirkin SJ, Varma VK, Walsh D, Wiersma D. (2001) Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry* 178:506-517.
- Kane J M, Eerdekens M, Lindenmayer J-P, Keith S J, Lesem M, Karcher K. (2003) Long-acting injectable risperidone: Efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 160:1125-1132
- Lambert M, Naber D. (2004) Current issues in schizophrenia: overview of patient acceptability, functioning capacity and quality of life. *CNS Drugs* 18 (Suppl 2): 5-17
- Leucht S, Pitschel-Walz G, Abraham D, Kissling W. (1999) Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* 35: 51-68
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO et al. for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353:1209-1223
- Macfadden W, Yi-Wen M, Haskins T, Bossie CA, Alphs L. (2010) A prospective study comparing the long-term effectiveness of injectable risperidone long-acting therapy and oral aripiprazole in patients with schizophrenia. *Psychiatry* 7: 23-31
- Novick D, Haro JM, Suarez D, Perez V, Dittman RW, Haddad PM. (2010) Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res* 176: 109-113

Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, *et al.* (2003) Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 60: 681-690

Taylor D. (2003) Aripiprazole: a review of its pharmacology and clinical use *Int J Clin Pract* 57: 49-54

Taylor D, Atkinson J, Fischetti C, Sparshatt A, Jones S. (2007) A prospective 6-month analysis of the naturalistic use of aripiprazole – factors predicting favourable outcome. *Acta Psychiatrica Scand* 116: 461-466

Taylor DM, Fischetti C, Sparshatt A, Thomas A, Bishara D, Cornelius V. (2009) Risperidone Long-Acting Injection: A prospective 3-year analysis of its use in clinical practice. *J Clin Psychiatry* 70:196-200

Tihonen J, Wahlbeck K, Lonnqvist J, Klaukka T, Ioannidis JPA, Volavka J, *et al.* (2006) Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *Br Med J*, 333: 224

Turner TH. (2004) Long term outcome of treating schizophrenia. *Br Med J* 329:1058

Young C, Taylor D. (2006) Health resource utilization associated with switching to risperidone long-acting injection. *Acta Psychiatrica Scand* 114: 14-20