Effectiveness of long-acting injectable antipsychotics: a clinical perspective

Enrico G Castillo,¹ T Scott Stroup²

¹Columbia University Medical Center, New York, New York, USA; ²Columbia University Medical Center and New York State Psychiatric Institute, USA

Correspondence to Dr T Scott Stroup; stroups@nyspi.columbia.edu

INTRODUCTION

The personal and societal costs of schizophrenia spectrum disorders are immense. Affected individuals may experience positive, negative and mood symptoms; medical and substance use comorbidities; and cognitive impairment that significantly impair social and occupational functioning. Globally, schizophrenia is a leading cause of years lost to disability, with a particularly large burden among adolescents and young adults.¹

Treatment of schizophrenia spectrum disorders aims at improved functioning and recovery across the lifespan, but symptom reduction and relapse prevention are important interim goals. Although antipsychotic medications reduce psychotic symptoms and greatly decrease the risk of relapse, their effectiveness in real-world practice is decreased by non-adherence.² A meta-analysis of studies that used trained personnel to measure antipsychotic medication adherence found that not 'regularly taking medications as prescribed' is prevalent in an average of 41% of participants across 10 studies.³ Despite this high prevalence, providers are often unaware of this issue and generally overestimate medication adherence in their patients.⁴

Long-acting injectable (LAI) formulations of antipsychotic medications were developed to improve adherence. The first LAIs, fluphenazine enanthate and decanoate, were introduced in 1966 in the context of large-scale deinstitutionalisation of patients with serious mental illnesses and the consequent need for effective community-based treatment. Numerous LAI antipsychotics have been developed and marketed in the meantime. Table 1 lists the LAI antipsychotic medications currently available in the USA and the UK.^{5 6}

LAIs reduce the frequency at which a patient has to decide whether to take medication. Rather than deciding to take a medication once or twice daily, the patient must only decide to have an injection administered once or twice monthly. Pharmacokinetically, LAIs provide a more stable steady-state concentration of medication in the blood compared with daily oral dosing.

Clinicians who are considered using LAIs in their practice want to know: Do LAIs improve patient outcomes compared with oral antipsychotics and if so, which outcomes? Are newer LAIs more effective than older ones? Who should receive LAIs? This review will draw lessons from decades of research that compares the effectiveness of LAIs to oral medications and to other LAIs.

LAIS VERSUS ORAL ANTIPSYCHOTIC MEDICATIONS: ADHERENCE

Numerous researchers have examined whether LAIs improve adherence as compared with oral medications, but there is no definitive answer. While LAIs decrease how often a patient has to decide whether to take a medication, they do not eradicate adherence issues, as patients may choose to discontinue the monthly or bimonthly injections.

Observational studies, though subject to confounding, provide suggestive evidence that LAIs improve medication adherence in routine practice.^{7–11} For example, Brnabic *et al*¹² conducted a post hoc analysis of a prospective observational study that collected data at 31 international sites. The study matched 40 participants taking an LAI to an equal number taking an oral antipsychotic medication. The study found that compared to those treated with LAIs, twice as many on oral medications switched, augmented or discontinued their medications.

Randomised controlled trials (RCTs), however, have not found improved adherence with LAIs.^{13–19} A systematic review and meta-analysis by Leucht *et al*²⁰ identified five RCTs that reported results on adherence and found no significant difference in adherence between those on LAIs and those on oral medications, although adherence was typically not measured rigorously. The methodological differences between observational studies and RCTs that may explain these conflicting findings are described below.

LAIS VERSUS ORAL MEDICATIONS: EFFECTIVENESS

The literature on LAIs and relapse prevention is also conflicting, as illustrated by two meta-analyses by the same research group. The first meta-analysis in 2011 collected outpatient RCTs that compared LAIs with oral antipsychotic medications and lasted for at least 12 months (10 studies, n=1700).²⁰ The analysis found that patients on LAIs are 30% less likely to relapse compared with those on oral antipsychotic medications. This translates to a number needed to treat of 10. The second meta-analysis in 2014 used a broader set of inclusion criteria, including inpatient and outpatient studies of at least 6-month duration, and included two new large studies that did not find an overall advantage for LAIs over oral medications. This will be discussed below.²¹ Contrary to the earlier study, this second meta-analysis (21 studies, n=5176) concluded that LAIs did not significantly reduce rates of

Table 1 Long-acting antipsychotic injectable medications available in the USA and the UK^{5 6}

Medication	Half-life (days)	Starting dose (mg)	Second dose (mg)	Maintenance dose (mg)
Aripiprazole extended release	29.9–46.5	400	400 (4 weeks later)	300–400 every 4 weeks
Flupenthixol decanoate	21	20 mg	20–40 mg (7 days later)	50–300 every 2–4 weeks
Fluphenazine decanoate	6–10	12.5	12.5–25 (6–14 days later)	12.5–50 every 2–3 weeks
Haloperidol decanoate	21	50	50–100 (3–28 days later)	50–200 every 3–4 weeks
Olanzapine pamoate/embonate	30	210–300	210–300 (2 weeks later)	150–300 every 2 weeks or 300–405 every 4 weeks
Paliperidone palmitate	25–49	234	156 (7 days later)	39–234 every 4 weeks
Pipotiazine palmitate	15	25 mg	25–50 mg (4–7 days later)	50–100 every 4 weeks
Risperidone microspheres	3–6	25	25–50 (2 weeks later)	25–50 every 2 weeks
Zuclopenthixol decanoate	19	100 mg	200–500 mg (7 days later)	200–500 mg every 1–4 weeks

relapse compared with oral antipsychotic medications, except in studies that used 'first-generation' antipsychotic LAIs and in studies published in 1991 or earlier. The authors postulate a number of reasons for the superiority of LAIs in these two subgroups, including changes over the decades in definitions and thresholds for relapse, differences between older and newer medications, and recent trends towards the use of lower doses of antipsychotic medications. Since there are striking differences in results between the two meta-analyses, the authors reanalysed the newer data using the same criteria as the first study. By now including the two large additional trials that lasted for more than 12 months and found no advantage for LAIs, this updated analysis showed no significant difference in relapse rates between LAIs and oral medications.

The two recent RCTs that were added to the earlier meta-analysis used slightly different approaches to compare the effectiveness of LAIs with oral medications in preventing relapse.^{19 22} The PROACTIVE study was a double-blind RCT at eight clinical sites that randomised 305 patients with schizophrenia or schizoaffective disorder and a history of an exacerbation in the past year to LAI risperidone or to a newer oral antipsychotic medication of their physician's choice.²² The primary outcomes were rates of relapse and hospitalisation over 30 months. In this broad sample of patients, the PROACTIVE trial found no significant difference between the LAI and oral groups in the primary outcomes of time to first relapse or time to first hospitalisation. Secondary analyses found that patients in the LAI group had greater improvements in some types of psychiatric symptoms.

In their discussion of the PROACTIVE study, Buckley *et al*²² highlighted methodological issues that may affect the comparative effectiveness research on LAIs versus oral antipsychotics. The authors noted that frequent study contacts, access to free study medications, implicit or explicit efforts to monitor adherence, and patient selection may lead to improved adherence to all medications in these studies. These factors, which are present in RCTs but not in routine practice, could diminish differences between LAIs and oral medications with respect to adherence and relapse prevention compared with what would be expected in usual community care.

The issue of patient selection deserves special focus. Clinical trials, due to the importance of informed consent, select patients who are willing to be enrolled in a clinical trial that involves medications, to have their adherence monitored, and to attend frequent appointments. This population may have greater insight into their illness, greater engagement with their providers, and less non-adherence than the usual patients whom providers would consider for LAI medications. In short, if LAI clinical trials select patients who are relatively adherent and stable, then it is possible that LAIs might have a different effect in the real-world patients with unstable illness who are often prescribed LAIs.²³

To address the issue of patient selection, Rosenheck *et al*¹⁹ conducted a 2-year study in the US Veterans Health Affairs system that specifically selected patients with unstable illness by including only those deemed at risk of psychiatric hospitalisation. The double-blind RCT included 369 individuals with schizophrenia who were assigned to LAI risperidone or the clinician's choice of oral antipsychotic medication. Similar to the PROACTIVE study, this study found no significant differences between LAIs and oral drugs in rates of psychiatric hospitalisations, psychotic symptoms, quality of life or social functioning.

Kirson *et al*²⁴ used meta-analyses to examine the influence of study design on the results of LAI versus oral antipsychotic medication comparative effectiveness research. The authors examined 12 studies that included 19 different LAI–oral medication combinations. They found no superiority of LAIs over oral medications in RCTs, but found significant benefits of LAIs over oral formulations in observational studies. To explain these findings, the authors highlight the tension between methodological rigour and real-world generalisability in RCTs and

observational studies, respectively. RCTs include methods to standardise the conditions between the LAI and oral medication arms such as adherence monitoring and frequent appointments. Kirson *et al* also describe a possible 'Hawthorne effect'—where behaviour is affected by the awareness of being observed—that would lead study subjects to have greater adherence to oral medications than they would have in real-world practice because of their knowledge that their adherence is being monitored. The authors conclude that these aspects of RCTs attenuate the advantages of LAIs over oral medications that are seen in observational studies.

Another issue is stage of illness. Some have argued that LAIs may be most beneficial when used for people experiencing a first episode of psychosis, when knowledge about the illness is low and ambivalence about medications is high. A large-scale study, using Finnish national health registries of 2588 participants after a first hospitalisation for schizophrenia, compared LAIs with oral antipsychotic medications in routine practice conditions.¹⁰ The authors found that those on LAI haloperidol, risperidone or perphenazine were significantly less likely to discontinue their medication ($p < 0.0001$) compared to those on the oral versions of these medications. When these results were pooled, they found that those on LAIs were 59% less likely to discontinue their medication up to 7 years of follow-up and 36% less likely to be rehospitalised within 2 years. Interestingly, these benefits have also been recently reported in a single-site RCT ($n = 83$) that compared oral with LAI risperidone among those with recent-onset schizophrenia.²⁵ In this study, those treated with the LAI had significantly lower rates of relapse (5% vs 33%) and were four times less likely to be hospitalised compared with those on the oral formulation. These two studies, a large-scale naturalistic study and an RCT, agree in their observations of substantial benefits of LAIs over oral medications in those with recent-onset schizophrenia.

OLDER LAIS VERSUS NEWER LAIS

Beginning with clozapine in 1989, a new wave of oral antipsychotic medications that came to be known as second-generation or atypical antipsychotics was released. The initial hope was that the newer medications would be more efficacious than the older antipsychotic medications. However, a considerable amount of research has called into question this initial assumption. For example, the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) schizophrenia trial found that several newer antipsychotic medications were not more effective than the older antipsychotic medication perphenazine.²⁶ Other comparative effectiveness trials and meta-analyses comparing newer with older oral antipsychotic medications have shown similar results.^{27–30} Research has shown that some of the newer antipsychotics are associated with a lower incidence of neurological side effects as well as high rates of metabolic adverse effects compared with older medications.^{31 32} Additionally, increasing evidence suggests that there is considerable variability among the older and newer drugs, which calls into question the validity of the 'generation' categories.^{28 33}

Few studies have looked at how newer LAIs are compared with older LAIs. Rubio *et al*³⁴ examined the effects of the drugs on substance use outcomes in an RCT of 115 individuals with schizophrenia and a substance use disorder. Participants were randomly assigned to risperidone LAI or zuclopenthixol LAI on an open-label basis for 6 months. The authors found those on LAI risperidone to have significantly fewer positive urine drug tests and significantly lower ratings on a psychotic symptom scale (positive and negative syndrome scale, PANSS) compared with those on zuclopenthixol LAI.

In contrast, a 2013 study by Lammers *et al*³⁵ found no significant difference between LAI risperidone and 'first-generation' LAIs. The authors conducted a single-site, outpatient retrospective comparative effectiveness study comparing those with schizophrenia spectrum illness on

risperidone LAI (n=70) versus 'first-generation' LAIs (n=102). Lammers *et al* found no significant differences between the groups for the primary outcomes of time to treatment discontinuation or hospitalisation, but did find that a higher incidence of extrapyramidal symptoms in patients on 'first-generation' LAIs.

Two recent multisite RCTs have taken on this question of newer versus older LAIs.^{36 37} A small trial by Covell *et al*³⁶ enrolled patients on haloperidol decanoate (n=40) or fluphenazine decanoate (n=22), and then randomised these patients to remain on their current LAI or switch to risperidone LAI. The study period was for 12 months, six of which followed a study protocol followed by 6 months of more naturalistic observation. The primary outcome was time to treatment discontinuation, with a number of secondary outcomes. The authors found that those randomised to switch to risperidone LAI had higher rates of treatment discontinuation and significantly greater increases in weight and prolactin levels.

McEvoy *et al*³⁷ conducted a large prospective comparative effectiveness trial of the newer LAI paliperidone palmitate to haloperidol decanoate. A Comparison of LAI Medications (ACLAIMS) was a double-blind RCT at 22 clinical sites. The patients (n=311) received LAI paliperidone or haloperidol monthly for as long as 24 months. Inclusion criteria explicitly required a history of medication non-adherence and/or substance use, both of which are risk factors for the primary outcome of efficacy failure. The authors defined efficacy failure as "a psychiatric hospitalisation, a need for crisis stabilisation, a substantial increase in frequency of outpatient visits, a clinician's decision that oral antipsychotic could not be discontinued within 8 weeks after starting the long-acting injectable antipsychotics, or a clinician's decision to discontinue the assigned long-acting injectable due to inadequate therapeutic benefit." The ACLAIMS trial found no significant difference in efficacy failure between those taking paliperidone palmitate and haloperidol decanoate. However, those in the paliperidone palmitate group had higher serum prolactin levels and gained weight, while the haloperidol decanoate group experienced more akathisia, used more antiparkinsonian medications and lost weight. In summary, ACLAIMS did not find that the newer LAI was superior to the older LAI, but found significant differences in side effects.

CONCLUSIONS

While researchers debate the most appropriate research design (RCTs vs observational studies) and whether to focus on all-comers or those with risk factors for medication non-adherence, clinicians still need answers to the questions posed earlier: Do LAIs improve patient outcomes compared to oral antipsychotics and if so, which outcomes? Are certain LAIs more effective than others? Who should receive LAIs? (box 1).

Although the evidence is conflicting and weaker than expected, we believe LAIs can play an important role in improving adherence and preventing hospitalisations. LAIs should be considered in those with risk factors for medication non-adherence, for example a history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications and poor insight.³⁸ By decreasing the number of times a patient has to decide to take a medication, and by promptly alerting clinicians and other providers to the onset of non-adherence when a patient misses a scheduled injection, LAIs are a useful part of the antipsychotic formulary.

Research to date is clear in showing no efficacy or overall effectiveness advantage of newer LAIs (risperidone and paliperidone) over older LAIs.^{36 37} We recommend that clinicians consider each patient's preferences, prior experience with antipsychotics, health status and the specific side-effect profiles of the medications when selecting an LAI antipsychotic.³⁹

Box 1 Summary of clinical perspective on long-acting injectable (LAI) antipsychotic medications

- ▶ Consider LAIs for patients with recent-onset schizophrenia and those with risk factors for medication non-adherence: history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications, and poor insight.
- ▶ When selecting an LAI, consider a patient's preferences, health status, experience with prior antipsychotic medication trials, and the side-effect profiles of different medications.
- ▶ The effectiveness of newer LAIs and older LAIs is similar.
- ▶ Clozapine rather than LAIs should be tried for those whose clinical instability is due to treatment-resistant illness rather than medication non-adherence.

Since recent-onset psychosis is an important opportunity to prevent relapses and clinical deterioration, LAIs may have an important role to play in this situation. However, we caution that this is also a time to use medications judiciously to help ensure that an individual's early encounters with medications are positive. For example, because the dosages of LAI antipsychotics are not immediately changeable, they are less convenient than oral medications when a dose reduction is indicated due to side effects. As people experiencing recent-onset psychosis are particularly sensitive to side effects, this is a disadvantage of LAIs in this situation.

Should LAIs be used for those with treatment-resistant schizophrenia? If medication non-adherence is not known or suspected, then the answer is no. For true treatment resistance, in which patients take but do not adequately benefit from antipsychotics, clozapine is the evidence-based choice.

In summary, in spite of equivocal evidence to support any advantages over oral medications, LAIs have a legitimate and potentially important role in clinical practice. We strongly recommend that clinicians include LAI antipsychotics in their armamentarium and offer them to patients with known or suspected poor adherence, and consider them for patients with recent-onset psychosis. However, in all the cases medications and medication adherence are only part of a comprehensive treatment plan to help patients achieve their goals.

Competing interests None.

doi:10.1136/eb-2015-102086

Received 23 February 2015; Accepted 11 March 2015

REFERENCES

1. Gore FM, Bloem PJ, Patton GC, *et al*. Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet* 2011;**377**:2093–102.
2. Leucht S, Tardy M, Komossa K, *et al*. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012;**379**:2063–71.
3. Lacro JP, Dunn LB, Dolder CR, *et al*. 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.
4. Byerly M, Fisher R, Whatley K, *et al*. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. *Psychiatry Res* 2005;**133**:129–33.
5. Joint Formulary Committee. *British National Formulary*. Pharmaceutical Press, 2013.
6. Lieberman JA, Stroup TS, Perkins DO. *Essentials of schizophrenia*. Washington DC: American Psychiatric Publishing, 2011.
7. Haro JM, Novick D, Belger M, *et al*. Antipsychotic type and correlates of antipsychotic treatment discontinuation in the outpatient treatment of schizophrenia. *Eur Psychiatry* 2006;**21**:41–7.

8. **Olivares JM**, Rodríguez-Morales A, Diels J, *et al*. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). *Eur Psychiatry* 2009;**24**:287–96.
9. **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**:603–9.
10. **Tiihonen J**, Wahlbeck K, Lonnqvist J, *et al*. 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. *BMJ* 2006;**333**:224.
11. **Zhu B**, Ascher-Svanum H, Shi L, *et al*. Time to discontinuation of depot and oral antipsychotics in the usual care of schizophrenia. *Psychiatr Serv* 2008;**59**:315–17.
12. **Brnabic AJ**, Kelin K, Ascher-Svanum H, *et al*. Medication discontinuation with depot and oral antipsychotics in outpatients with schizophrenia: comparison of matched cohorts from a 12-month observational study. *Int J Clin Pract* 2011;**65**:945–53.
13. **Arango C**, Bombin I, Gonzalez-Salvador T, *et al*. Randomised clinical trial comparing oral versus depot formulations of zuclopenthixol in patients with schizophrenia and previous violence. *Eur Psychiatry* 2006;**21**:34–40.
14. **Bai YM**, Ting Chen T, Chen JY, *et al*. Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective, single-blind pharmacokinetic study. *J Clin Psychiatry* 2007;**68**:1218–25.
15. **Chouinard G**, Annable L, Steinberg S. A controlled clinical trial of fluspirilene, a long-acting injectable neuroleptic, in schizophrenic patients with acute exacerbation. *J Clin Psychopharmacol* 1986;**6**:21–6.
16. **Chue P**, Eerdekens M, Augustyns I, *et al*. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *Eur Neuropsychopharmacol* 2005;**15**:111–17.
17. **Kane JM**, Detke HC, Naber D, *et al*. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry* 2010;**167**:181–9.
18. **Keks NA**, Ingham M, Khan A, *et al*. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. *Br J Psychiatry* 2007;**191**:131–9.
19. **Rosenheck RA**, Krystal JH, Lew R, *et al*. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 2011;**364**:842–51.
20. **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.
21. **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.
22. **Buckley PF**, Schooler NR, Goff DC, *et al*. Comparison of SGA oral medications and a long-acting injectable SGA: the PROACTIVE Study. *Schizophr Bull* 2015;**41**:449–59.
23. **Shi L**, Ascher-Svanum H, Zhu B, *et al*. Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. *Psychiatr Serv* 2007;**58**:482–8.
24. **Kirson NY**, Weiden PJ, Yermakov S, *et al*. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. *J Clin Psychiatry* 2013;**74**:568–75.
25. **Nuechterlein K**. Oral versus injectable risperidone for treating first-episode schizophrenia. NCT00330551. 2013. 8 Nov 2014. <http://clinicaltrials.gov/ct2/show/NCT00330551?term=nuechterlein&rank=5>
26. **Goff DC**, Sullivan LM, McEvoy JP, *et al*. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res* 2005;**80**:45–53.
27. **Jones PB**, Barnes TR, Davies L, *et al*. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CULASS 1). *Arch Gen Psychiatry* 2006;**63**:1079–87.
28. **Leucht S**, Corves C, Arbter D, *et al*. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;**373**:31–41.
29. **Rosenheck R**, Lin H. Noninferiority of perphenazine vs. three second-generation antipsychotics in chronic schizophrenia. *J Nerv Ment Dis* 2014;**202**:18–24.
30. **Rosenheck R**, Perlick D, Bingham S, *et al*. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA* 2003;**290**:2693–702.
31. **Newcomer JW**. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005;**19**(Suppl 1):1–93.
32. **Citrome LL**. The increase in risk of diabetes mellitus from exposure to second-generation antipsychotic agents. *Drugs Today (Barc)* 2004;**40**:445–64.
33. **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**:951–62.
34. **Rubio G**, Martinez I, Ponce G, *et al*. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. *Can J Psychiatry* 2006;**51**:531–9.
35. **Lammers L**, Zehm B, Williams R. Risperidone long-acting injection in schizophrenia spectrum illnesses compared to first generation depot antipsychotics in an outpatient setting in Canada. *BMC Psychiatry* 2013;**13**:155.
36. **Covell NH**, McEvoy JP, Schooler NR, *et al*. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. *J Clin Psychiatry* 2012;**73**:669–75.
37. **McEvoy JP**, Byerly M, Hamer RM, *et al*. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA* 2014;**311**:1978–87.
38. **Byerly MJ**, Nakonezny PA, Lescouffair E. Antipsychotic medication adherence in schizophrenia. *Psychiatr Clin North Am* 2007;**30**:437–52.
39. **Goff DC**. Maintenance treatment with long-acting injectable antipsychotics: comparing old with new. *JAMA* 2014;**311**:1973–4.