PrescQIPP Community Interest Company

Antipsychotic drugs

This bulletin focuses on drugs for psychosis. There are numerous antipsychotic drug (APD) preparations on the market that vary widely in acquisition costs. Across England and Wales over £85 million is spent annually on atypical antipsychotics. Of this £27.4 million is spent annually on quetiapine XL products (based on ePACT December 2015 to February 2016).

This bulletin is a resource for GPs to aid local discussion to agree prescribing choices. Recommendations are included for switching from quetiapine XL to quetiapine immediate release (IR). Organisations may also wish to consider prescribing a modified release branded generic as a cost effective option when an IR preparation is not suitable. Further recommendations include a review of olanzapine lyophilisates tablets to orodispersible tablets and risperidone orodispersible to standard risperidone tablets as appropriate. Support material is available on the PrescQIPP website: http://www.prescqipp.info/resources/viewcategory/248-antipsychotic-drugs

This bulletin does not cover prescribing of antipsychotic drugs in dementia which should not be used long term. Please refer to the review of antipsychotic drugs in dementia toolkit (T7).

PrescQIPP also acknowledges Hertfordshire Partnership Trust for sharing their resources.

Recommendations

- First line choice of an APD should be from a locally agreed formulary where possible. Involvement from mental health trust clinicians and medicines management teams is essential and will facilitate implementation.
- Choice should be based on indication, product licensing, co-morbidities, risk factors, likely benefits, side effect profile, cost, previous patient response and individual patient preference. The choice of medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees.
- Local trust policy needs to be established for patients initiated on quetiapine. Quetiapine IR is the preferred option. Exceptions include acutely unwell patients in whom the simplified titration and rapid dose escalation of the XL formulation (to achieve a therapeutic dose) can be used for the first three days, after which the IR preparation may be used. The XL formulation may be preferred if intolerable side effects develop with the IR formulation, e.g. sedation and hypotension.
- Patients currently stabilised on the quetiapine XL formulation should, where possible, be switched to the quetiapine IR twice daily formulation in line with local trust policy unless there are compelling clinical reasons not to do so, e.g. side effects and compliance where twice daily adherence to therapy may cause a problem. In discharge letters, psychiatrists should advise on the clinical justification of using an XL preparation if these are to be continued.
- If once daily quetiapine XL is needed, organisations may wish to consider prescribing a modified release branded generics as a cost effective option; Biquelle® XL, Zaluron® XL, Sondate® XL and Mintreleq® XL have the lowest cost.
- Tablet formulations of APDs are preferred to dispersible and liquid formulations. Prescribe as dispersible preparations only if there are problems swallowing or in patients with compliance issues.

- Review patients currently on dispersible tablets for suitability of switching to standard tablets, i.e. olanzapine orodispersible or lyophilisates to standard tablets and risperidone orodispersible to standard tablets.
- If a soluble olanzapine formulation is needed, prescribe as generic olanzapine orodispersible tablets. Switch patients from olanzapine lyophilisates to orodispersible.
- As with all switches, these should be tailored to the individual patient.

Background

Schizophrenia is a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms that alter a person's perception, thoughts, affect and behaviour. It is widely accepted that there is very little difference in efficacy between the approved APDs (except clozapine). However, there are notable differences in their side-effect profiles and more recently, due to patent expiries, significant variations in their cost. The National Institute for Health and Care Excellence (NICE CG) 178[1] on psychosis and schizophrenia in adults states that there was very little evidence of clinically significant differences in efficacy between the oral antipsychotic drugs examined and recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. NICE recommends providing information and discussing the likely benefits and possible side effects of each drug, including:[1]

- Metabolic (including weight gain and diabetes)
- Extrapyramidal (including akathisia, dyskinesia and dystonia)
- Cardiovascular (including prolonging the QT interval)
- Hormonal (including increasing plasma prolactin)
- Other (including unpleasant subjective experiences).

An oral APD should be offered first line unless the patient prefers a depot/long acting injection (LAI) after an acute episode or when avoiding covert non-adherence to antipsychotic treatment is a clinical priority.[1] Standard tablets of oral formulations are preferred. Orodispersible tablets and liquid formulations should only be used when clinically essential.

There is no first line APD which is suitable for all patients. When making prescribing decisions, clinicians are expected to take into account many factors including the cost impact an APD choice will have on the wider health economy. Algorithm includes the important factors to be considered when selecting an APD for schizophrenia. Table 1, on page 4, provides a list of antipsychotics and available formulations. APDs are also often used in the management of other mental health disorders and the same considerations should be applied when selecting an APD in these situations too.

Algorithm 1: Antipsychotic treatment algorithm for schizophrenia (Taken from Hertfordshire Partnership Trust, adapted from the Maudsley Prescribing Guidelines in Psychiatry 11th Edition)[2]

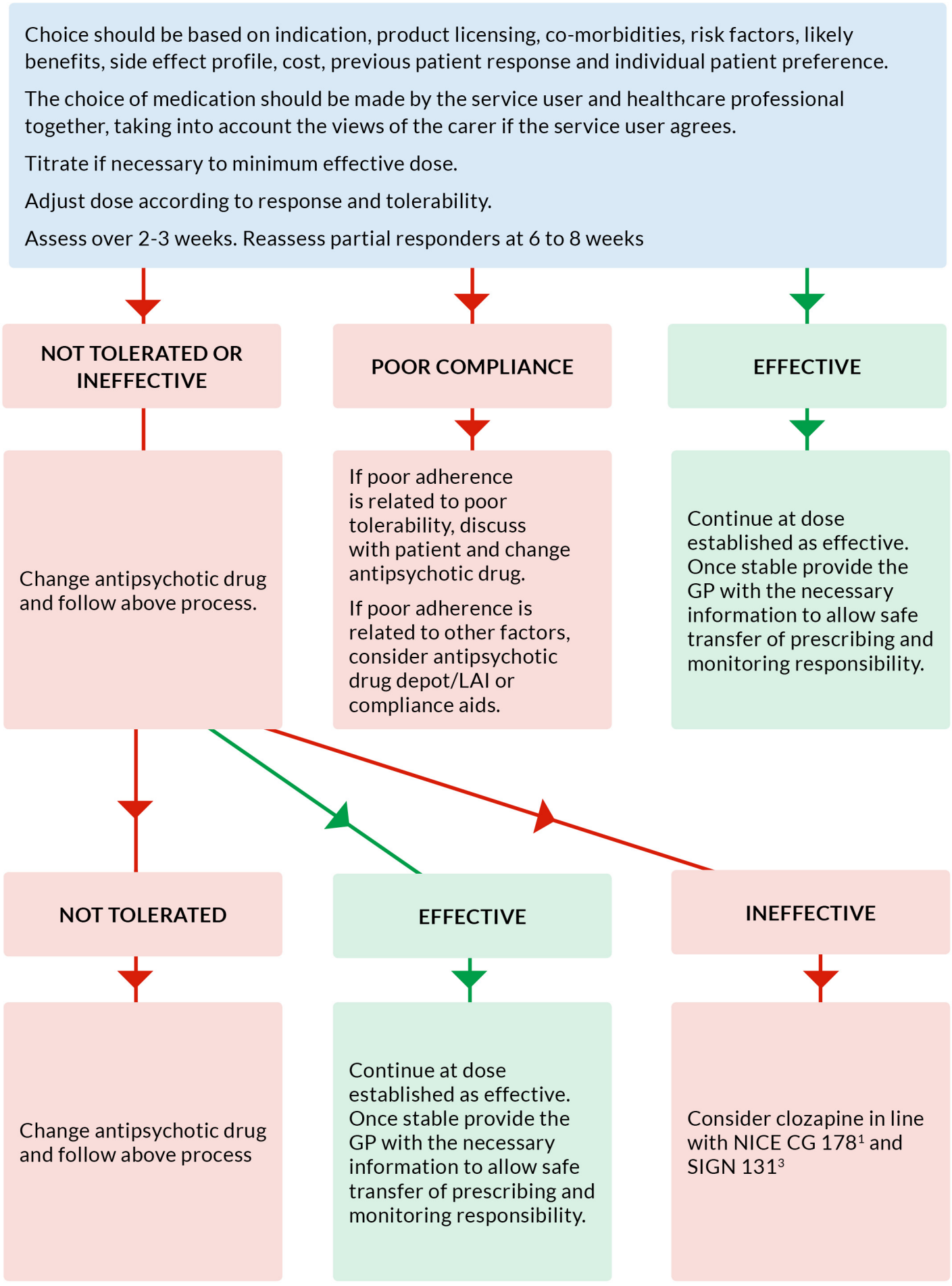


Table 1: Antipsychotic drug formulations

Drug		Formulation
First generation antipsychotics	Amisulpiride	Oral
	Chlorpromazine	Oral (Note : injection – acute situation only, suppositories – unlicensed special)
	Flupenthixol	Oral, depot injection
	Fluphenazine	Depot injection
	Haloperidol	Oral, depot injection
	Promazine	Oral
	Sulpiride	Oral
	Trifluoperazine	Oral
	Zuclopenthixol	Oral, long acting injection (LAI)
Second generation antipsychotics	Aripiprazole	Oral, long acting injection (LAI)
	Clozapine	Oral
	Olanzapine	Oral, long acting injection (LAI)
	Paliperidone	Oral, long acting injection (LAI)
	Quetiapine	Oral
	Risperidone	Oral, long acting injection (LAI)

Adverse effects

Table 2, on page 7, provides a comparison of the relative side effects of APDs and can be used by prescribers in conjunction with patients and carers to help guide choice of APD. Graphs 1 and 2, on pages 8 and 9, provide a cost comparison of APDs.

APDs are associated with a wide range of adverse effects, e.g. extrapyramidal side effects (EPSE), dry mouth, blurred vision and constipation, feelings of dizziness or light headedness; and weight gain. Though rare, they can also cause more serious side effects such as diabetes or metabolic syndrome, neuroleptic malignant syndrome, and cardiac arrhythmia. There is a clear increased risk of stroke and a small increased risk of death when antipsychotics (first or second generation) are used in elderly people with dementia.[4]

Cardiac side effects

Antipsychotics can also increase the risk of venous thromboembolism (VTE). The absolute risk is about four extra cases per 10,000 patients per year for patients of all ages.[5] In view of the serious consequences, risk of VTE is an important factor to consider when prescribing antipsychotics before and during treatment, especially to those people who are at high risk; preventative measures for VTE should be taken where necessary.

Antipsychotics can cause prolongation of the QT interval. Concomitant use with other drugs also known to prolong the QT interval is not recommended and is cautioned in congestive heart failure, cardiac hypertrophy, hypokalaemia or hypomagnesaemia.[6]

Haloperidol, aripiprazole, olanzapine, paliperidone, pimozide and risperidone should be avoided in congenital long QT.[6]

Hyperglycaemia

Treatment with APDs is associated with impaired glucose metabolism, exacerbation of existing type 1 and 2 diabetes, new-onset type 2 diabetes mellitus, and diabetic ketoacidosis, (a severe and potentially fatal metabolic complication). The strength of the association between antipsychotics and diabetes varies across individual medications, with the largest number of reports for chlorpromazine, clozapine and olanzapine.[7]

Hyperlipdaemia

Risperidone and aripiprazole appear to be associated with a relatively low risk for hyperlipidemia, whereas quetiapine, olanzapine and clozapine are associated with a relatively high risk for hyperlipidemia.[8] Possible underlying causes of lipid dysregulation include weight gain, dietary changes, and glucose intolerance. Given the multiple cardiovascular risk factors reported for patients with schizophrenia, great care must be exercised to minimize the additional risk for hyperlipidemia when choosing antipsychotic therapy.

NICE recommends that if a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance on obesity, lipid modification and preventing type 2 diabetes.[9,10,11]

Initiation and titration

Treatment with an APD should be considered as an explicit individual therapeutic trial, which includes the following elements:[1]

- Discuss and record the side effects that the person is most willing to tolerate.
- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upward within the dose range given in the British National Formulary (BNF) or summary of product characteristics (SPC).
- Justify and record reasons for dosages outside the range given in the BNF or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks.
- For ‘as required’ prescriptions, review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check if doses exceed the maximum specified in the BNF or SPC.
- Do NOT use a loading dose of antipsychotic medication.
- Do NOT initiate regular combined antipsychotic medication, except for short periods.

Monitoring

Sufficient clinical information, including choice of drug, dose, formulation, rationale for APD choice and monitoring requirements must also be provided so that the GP can safely take on prescribing responsibility.[1] NICE recommends that monitoring should be the responsibility of the secondary care team for at least the first 12 months or until the person’s condition has stabilised. Continued usage may

be through a shared care agreement across the primary and secondary care interface. Recommendations are to monitor and record the following factors regularly throughout treatment, but especially during titration:

- Response to treatment, including changes in symptoms and behaviour.
- Side effects of treatment.
- The emergence of movement disorders.
- Weight; weekly for six weeks, at 12 weeks, at 12 months then annually (plotted on a chart).
- Waist circumference; annually (plotted on a chart).
- Pulse and blood pressure; at 12 weeks, at 12 months then annually.
- Fasting blood glucose, HbA1c, and blood lipid levels at 12 weeks, at one year and then annually.
- Adherence and physical health.

Clozapine

Clozapine is licensed for treatment resistant schizophrenia. Clozapine may be considered for patients who have not responded to two atypical antipsychotics; at least one of which should be a non-clozapine second-generation antipsychotic.[1]

1-2% of patients taking clozapine may suffer neutropenia leading to agranulocytosis. Regular full blood counts are conducted for all patients taking clozapine, co-ordinated by a centralized monitoring service.[12] Clozapine is contraindicated with other drugs known to have a substantial potential to cause agranulocytosis, e.g. carbamazepine, oxcarbazepine, penicillamine, methotrexate and chemotherapy.

Prescribers should also be aware of the potential of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine i.e. sudden smoking cessation may increase plasma clozapine levels and may lead to adverse effects; a dosage adjustment of clozapine may be required.

If response to clozapine is inadequate, consider further review, including measuring therapeutic drug levels, before adding a second antipsychotic to augment treatment with clozapine. Choose a drug that does not potentiate the common side effects of clozapine.

A trial of augmentation may need to be up to eight to ten weeks.[1] Prescribing of clozapine should remain within the mental health trust unless locally agreed protocols are in place.

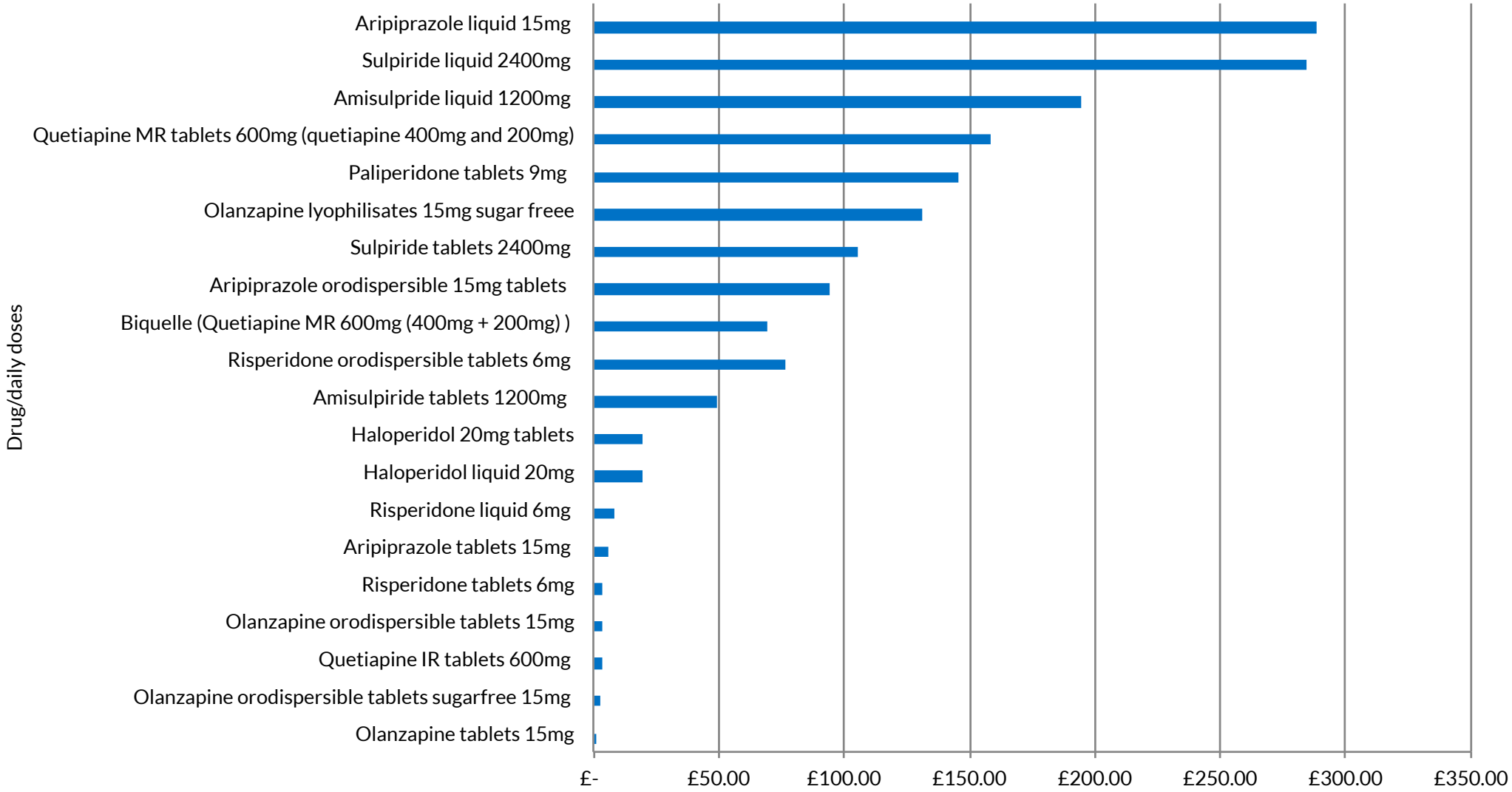
Table 2: Antipsychotic relative side effects[13]

		Anticholinergic effects	EPSE	Hypotension	Sedation	Weight gain	Prolactin elevation	Proconvulsant
Oral treatments	Haloperidol	••	•••	•	•	•	•••	• ?
	Olanzapine	•	o	o	••	•••	•	••
	Quetiapine (IR)	•	o	•	•	•	•	•
	Risperidone	•	•	•	• ?	•	••	o
	Sulpiride	•	•	o	•	•	••	o ?
	Amisulpride	• •	•	o	O	•	••	• ?
	Aripiprazole	o	o	o	O	•	o	o
	Chlorpromazine	••	••	•••	•••	•••	••• ?	•••
	Clozapine	••	o	•	•••	• ••	o	•••
	Flupentixol	••	• •	o	•	•		• ?
	Promazine	••	•	••	••	?	••• ?	
	Trifluoperazine	•••	••	•	•	?	••• ?	•
	Zuclopenthixol	••	•••	•	••	?		o ?
	Paliperidone	•	•	o	•	•	••	o ?
Depot injections	Flupenthixol IM	••	••	o	•	?		• ?
	Fluphenazine IM	••	•••	•	••	•	••• ?	•
	Haloperidol IM	•	•••	•	•	•	•••	•
	Zuclopenthixol	•••	•••	•	••	?		o ?
	Paliperidone	o	•	•	•	•	• •	o
	Risperidone consta	o	•	•	• ?	•	• •	o
	Aripiprazole	o	o	o	O	•	o	o

••• marked effect •• moderate effect • mild/transient effect o little or minimal effect ? no information available or little reported

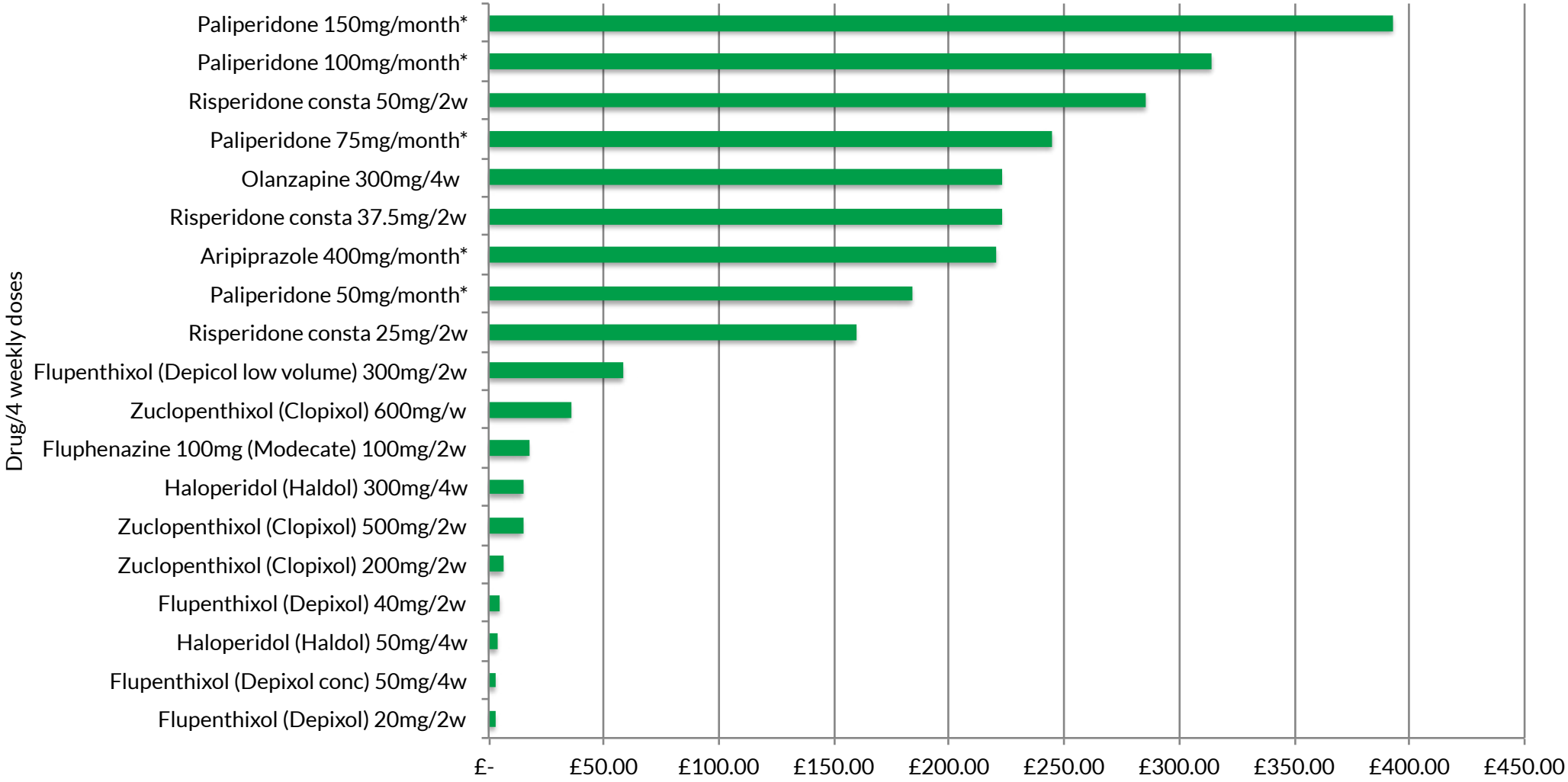
Graph 1: Comparison of 28 day oral antipsychotic costs based on maximum licensed doses at Drug Tariff prices[14,15]

N.B. Doses quoted do not imply equivalence



Graph 2: Antipsychotic depot and LAI comparative costs for 28 days treatment[14,15]

N.B. Doses quoted do not imply equivalence



New antipsychotic drugs

Paliperidone prolonged release tablets

Paliperidone is the active metabolite of risperidone.[16] A Cochrane review found its adverse effects to be similar to those of its parent compound, risperidone, with movement disorders, weight gain and tachycardia all more common with paliperidone than placebo.[17] A single study of six days duration found neither an advantage nor disadvantage of paliperidone compared to risperidone.[18] It should be noted that its use is not supported by most CCGs as the acquisition cost is significantly higher than risperidone. The patent for paliperidone tablets has expired however as yet there has been no UK launch of generic versions.[19]

Paliperidone long acting injection (LAI)

Paliperidone (as the palmitate salt) in a LAI preparation is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.[20]

Paliperidone has demonstrated non inferiority to risperidone LAI. In a 53-week, non-inferiority study where patients were randomised to four-weekly paliperidone LAI or two-weekly risperidone LAI and the primary outcome was change from baseline to end point in the total positive and negative syndrome score (PANNS). The trial failed to demonstrate non-inferiority to risperidone LAI, however, the authors concluded that this was because patients had not been given an initial loading dose of paliperidone. A second 13-week double blind non-inferiority study showed that paliperidone LAI was non-inferior to risperidone LAI with regard to difference in mean PANNS total scores.[21]

A Cochrane review found the adverse effects of paliperidone palmitate LAI to be similar to those of its related compounds, oral paliperidone, oral risperidone and risperidone LAI, with extrapyramidal movement disorders, weight gain, and tachycardia all more common with paliperidone palmitate than placebo. While no difference was found in the incidence of reported adverse sexual outcomes, paliperidone palmitate is associated with substantial increases in serum prolactin. When flexibly dosed with mean doses of approximately 70-110 mg every four weeks, paliperidone palmitate appears comparable in efficacy and tolerability to risperidone LAI flexibly dosed with mean doses of approximately 35mg every two weeks.[22]

Paliperidone palmitate LAI has the advantage that it does not require refrigeration or reconstitution.[20] Paliperidone palmitate offers some advantages in terms of tolerability, simplicity of treatment initiation and long duration, i.e. monthly injections.[23,24] The consensus of the authors in one of these reviews is that rather than reserving paliperidone palmitate for use in difficult-to-treat or refractory patients, it could be used to promote adherence and prevent relapse earlier in the course of the illness.[23] Taking into account the significantly higher cost, its use is only supported by some CCGs where the following advantages over risperidone would be of significant benefit: monthly administration, quicker onset of action, seven day flexibility to avoid missed doses, smaller administration volume, fewer drug interactions, wider dosing range and no dosage adjustment required in mild to moderate hepatic impairment. Usage would have to be in line with trust policy across the primary and secondary care interface.

Aripiprazole long acting injection (LAI)

Aripiprazole LAI (launched in UK in January 2014) is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole. The recommended starting and maintenance dose is 400mg and titration of the dose is not required. It should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).[25] The NICE evidence summary states that in a double-blind RCT (n=403), aripiprazole prolonged-release injection statistically significantly delayed time to impending relapse compared with placebo ($p<0.0001$). In a double-blind

RCT (n=662), aripiprazole prolonged-release injection was non-inferior to oral aripiprazole 10-30 mg daily for the proportion of participants experiencing impending relapse (7.12% and 7.76% respectively).[26]

No RCTs have directly compared aripiprazole prolonged-release injection with other antipsychotics.[26]

The place in therapy for this treatment is likely to be as an alternative treatment option to the currently available second-generation prolonged-release depot antipsychotics for maintenance treatment of schizophrenia. Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual factors for people with schizophrenia, when making decisions about using aripiprazole prolonged-release injection.

As the patent for aripiprazole tablets has now expired, cost savings can be realised by prescribing aripiprazole as a generic in line with its licensed indication for different generic products (see table 3). The 5-15mg strengths are virtually flat priced at £6.35 – £6.42 for 28 days supply. It is important to ensure that the dose is optimised on dosage escalation. 30mg aripiprazole is priced at £109.82.[14]

Table 3: Licensed indications of aripiprazole preparations

Preparation	Indication
Abilify[27]	Treatment of schizophrenia in adults and in adolescents aged 15 years and older.
Aripiprazole Pharmathen[28]	Treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment
Aripiprazole Sandoz[29]	Treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older
Ariprazole Dr Reddys[30]	Treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Lurasidone

Lurasidone is a second generation APD that can be used to treat schizophrenia in adults aged 18 years and over.[31] The NICE evidence summary is based on two RCTs.[32] From these two studies, both of which have limitations, lurasidone appears to be statistically significantly more effective than placebo and of similar effectiveness to olanzapine and risperidone. In both studies, lurasidone appeared to have a low potential for causing adverse weight and metabolic effects. The most common adverse effects (>10%) were akathisia, headache, somnolence, nausea, sedation, insomnia, anxiety and agitation. Although its place in therapy is not clear, it is likely that lurasidone will represent an additional treatment option alongside other antipsychotics.

Switching options and savings available

In England and Wales (ePACT December 2015 to February 2016), over £85 million was spent on atypical APDs over the course of a year.

For all the switching and savings options listed below, a 100% achievement may not be possible and switching would be dependent on patient factors, buy in from the clinicians and local agreement.

Quetiapine

Since the patent for Seroquel expired in 2012, generic quetiapine has been available in two dosage forms: quetiapine immediate release (IR) and quetiapine modified release (XL). There is a significant price difference between the two formulations and there is scope to achieve substantial cost savings by changing from XL to IR. These costs are detailed in table 4.

Switching from quetiapine XL (including Seroquel XL) to quetiapine IR **could save £26.5 million nationally over 12 months** (ePACT December 15 to February 2016). This is equivalent to £43,700 per year per 100,000 patients.

The licensed indications are as follows:[33,34]

- Quetiapine XL – ONCE daily
  - Treatment of schizophrenia, including prevention of relapse
  - Treatment of mania or depression in bipolar disorder
  - Prevention of relapse in bipolar disorder
  - Add on treatment (to an antidepressant) in major depressive disorder who have had suboptimal response to antidepressant therapy.
- Quetiapine IR – TWICE daily
  - Treatment of schizophrenia including prevention of relapse
  - Treatment of mania in bipolar disorder
  - Prevention of relapse in bipolar disorder
- Quetiapine IR – ONCE daily
  - Depression in bipolar disorder

The pharmacokinetics of the two formulations are similar: although the IR and XL reach the same peak plasma concentration (Cmax), the time taken to reach peak plasma concentration after administration is 1.5 hours for IR and 6 hours for XL.[33,34]

There is very little difference in terms of side effects between quetiapine XL and quetiapine IR. There may however be patients who do not tolerate quetiapine IR but are able to tolerate XL which could justify the use of the XL formulation. Although unlicensed in schizophrenia as a once daily preparation, there are two small short term studies supporting quetiapine IR once daily and this is occasionally done in practice.[35,36,37] A further Finnish retrospective study also evaluated the place in therapy of quetiapine XL and IR. The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) also allows monitoring of side effects.[38] http://egret.psychol.cam.ac.uk/medicine/scales/dubious/LUNSERS.pdf

Quetiapine XL

- If an IR preparation is deemed unsuitable consider a switch to a branded generic modified release preparation in line with organisation policy. Branded generic quetiapine products are less costly than generic products. The British National Formulary does recommend that modified release preparations should be prescribed by brand.[39]
- There are local debates on the prescribing of branded generics. The Pharmaceutical Services Negotiating Committee notes that, the savings incurred by specific “branded generics” are often unsustainable by the manufacturer which in the long term can impact on the financial viability of the pharmacy and put the provision of pharmaceutical care at risk. It states that the reduction in prices at a local level may actually cause increased prices for the NHS as a whole, as adjustments are made to ensure full delivery of total agreed pharmacy funding. This adjustment is applied nationally, so the adjustment may not restore viability to seriously affected local pharmacies. Frequent changes to prescribing could also be detrimental to patient care. Continually changing brands can create confusion for patients and can undermine their confidence in their medicines. As a result it is important to ensure clear policies on the prescribing of these branded generics and to ensure availability of these products.[40]
- There are currently seven different brands of quetiapine XL available: Biquelle®XL, Ebesque®XL, Zaluron® XL, Sondate® XL, Tenprolide® XL, Atrolax® XL and Mintreleq® XL
- The pharmacokinetic properties of these preparations are the same as that of the original brand Seroquel. They are also available in all 5 strengths except for Ebesque® XL and Atrolax® Xl which are not available as 150mg XL.[41-47]
- Biquelle® XL, Zaluron® XL, Mintreleq® XL and Sondate® XL have the lowest cost. The costs of these products are detailed in table 5.

- For organisations wishing to prescribe branded generics as a cost effective option switching from quetiapine XL (including Seroquel® XL) to the most cost effective quetiapine XL preferred preparations (i.e. Zaluron® XL, Biquelle® XL, Sondate® XL or Mintreleq® XL) could save £10.3 million nationally over 12 months. This is equivalent to £16,979 per year per 100,000 patients (ePACT December 15 to February 16).

Table 4: Comparison of quetiapine costs[14]

Quetiapine XL	Drug Tariff cost per 28 days	Quetiapine IR	Drug Tariff cost per 28 days
Quetiapine 50mg XL daily	£31.57	Quetiapine 25mg twice daily	£1.15
Quetiapine 150mg XL daily	£52.78	Quetiapine 75mg twice daily (3 x 25mg twice daily)	£3.44
Quetiapine 200mg XL daily	£52.78	Quetiapine 100mg twice daily	£1.85
Quetiapine 300mg XL daily	£79.33	Quetiapine 150mg twice daily	£2.34
Quetiapine 400mg XL daily	£105.56	Quetiapine 200mg twice daily	£2.59
Quetiapine 600mg XL daily (400mg and 200mg)	£158.34	Quetiapine 300mg twice daily	£3.31
Quetiapine 800mg XL daily (2 x 400mg daily)	£211.12	Quetiapine 400mg twice daily (2 x 200mg twice daily)	£5.18

Table 5: Comparison of Quetiapine XL brands (28 day cost)

Product/ Cost	Drug tariff[14]	Ebesque® XL15	Zaluron® XL15	Biquelle ® XL15	Mintreleq® XL15	Sondate® XL15	Tenprolide® XL15	Atrolax® XL
Quetiapine 50mg XL daily	£31.57	£14.84	£13.06	£13.74	£13.74	£13.05	£31.57	£31.57
Quetiapine 150mg XL daily	£52.78	n/a	£21.92	£23.08	£23.08	£21.92	No	No
Quetiapine 200mg XL daily	£52.78	£24.80	£21.92	£23.08	£23.08	£21.92	£52.78	£52.76
Quetiapine 300mg XL daily	£79.33	£37.29	£33.01	£34.74	£34.74	£33.00	£79.33	£79.33
Quetiapine 400mg XL daily	£105.56	£49.61	£43.87	£46.18	£46.18	£43.86	£105.56	£105.56

Actions

Local trust policy should be established for patients initiated on quetiapine. Quetiapine IR is the preferred option. Exceptions include acutely unwell patients in whom the simplified titration and rapid dose escalation of the XL formulation (to achieve a therapeutic dose) can be used for the first three days after which the IR preparation should be used. The XL formulation may be preferred if intolerable side effects develop with the IR formulation, e.g. sedation and hypotension.

Patients currently stabilised on quetiapine XL formulation should where possible be switched to the IR twice daily formulation in line with local trust policy unless there are compelling clinical reasons not to do so, e.g. side effects, compliance where twice daily adherence to therapy may cause a problem. If adherence with a twice a day treatment regimen with the IR formulation is likely to be a problem then a once a day regimen using IR tablets could be considered although this will be an unlicensed indication except for those with the depressive episode in bipolar disorder. See table 4 on page 14 for suggested dosage conversions.

In the depressive episodes of bipolar disorders, quetiapine IR may be prescribed once daily in the evening as this usage is licensed (in schizophrenia, once daily quetiapine IR is unlicensed).

The switch from quetiapine XL to IR may be associated with a slightly higher risk of sedation and postural hypotension. If these are a concern or the patient is at risk, then a larger proportion of the dose may be taken in the evening. Patients at increased risk of experiencing sedation or postural hypotension following the switch to quetiapine IR may include the elderly, adolescents, patients with concurrent cardiac medication and concurrent CNS depressants. Table 6 provides details of suggested dosing regimens.

It will be necessary for each CCG to gain consensus as to how the switch is communicated to mental health specialists. It may be necessary to seek the approval of the relevant psychiatrist before making the switch or for the patient to be referred to the psychiatrist who can make the decision to switch. If agreed locally, GP practices can send a list of patients to the local psychiatrist for agreement before a switch is undertaken. In discharge letters, psychiatrists should advise on the clinical justification of using an XL preparation if these are to be continued. If an XL preparation is needed, this should be prescribed by the preferred quetiapine XL brand (as agreed by the CCG and mental health trust). Biquelle® XL, Zaluron® XL, Sondate® XL and Mintreleq® XL have the lowest cost.

All changes to medication must be fully discussed, explained and agreed with the patient (and or their carer as appropriate). A patient information leaflet is available to help explain the reasons for the switch (Attachment 1). The first dose of the IR formulation should be given approximately 24 hours after the last dose of the XL formulation.

Table 6: Suggested dose conversion when switching from quetiapine XL to IR

Current dose quetiapine XL	**Quetiapine IR dosing options**		
	Patients who are tolerating quetiapine well and do not have compliance concerns	**Patients who are (or at risk of) experiencing sedation or postural hypotension following the switch**	**Patients who are tolerating quetiapine well but have compliance concerns.** **IR is ONLY licensed once daily in patients with depressive episodes in bipolar manic disorders**
100mg XL daily	50mg twice daily	25mg in the morning, 75mg at night	100mg at night
200mg XL daily	100mg twice daily	50mg in the morning, 150mg at night	200mg at night
300mg XL daily	150mg twice daily	100mg in the morning, 200mg at night	300mg at night
400mg XL daily	200mg twice daily	150mg in the morning, 250mg at night	400mg at night
600mg XL daily	300mg twice daily	200mg in the morning, 400mg at night	600mg at night
800mg XL daily	400mg twice daily	No change	No change

Olanzapine lyophilisates

Review the patient to consider if soluble tablets are needed and a switch to standard tablets would be possible. Only use a soluble form if there are swallowing difficulties, patient is PEG fed or for patients with compliance issues. Rates and extent of absorption of both preparations are comparable.[48]

It is acknowledged that some patients may be monitored and supervised at home which may necessitate the use of orodispersible preparations to minimized the risk of patients "cheeking" tablets and disposing of them later.

If a patient requires orodispersible olanzapine, the most cost effective version to prescribe is generic olanzapine orodispersible tablets (rather than lyophilisates).

Switching from olanzapine lyophilisates to olanzapine orodispersible **could save £1.7 million nationally over 12 months. This equates to £2,796 per year per 100,000 patients**.

Table 7: Comparison of olanzapine costs (28 day costs)[14,15]

Olanzapine	Tablets	Oral lyophilisates sugar free	Orodispersible tablets	Orodispersible tablets sugar free
5mg	£1.03	£48.07	£2.54	£1.85
10mg	£1.25	£87.40	£2.50	£2.50
15mg	£1.45	£131.10	£3.20	£3.11
20mg	£1.69	£174.79	£4.32	£4.60

Risperidone

Review if risperidone orodispersible tablets are necessary.

Only use orodispersible tablets if the patient has swallowing difficulties, to prevent "cheeking" or for patients with compliance issues. Otherwise consider switch to plain risperidone tablets.

Switching from risperidone orodispersible to risperidone standard tablets **could save £1.4 million nationally over 12 months. This equates to £2,363 per year per 100,000 patients** (ePACT December 15 to February 16).

Table 8: Comparison of risperidone costs (28 tablet costs)[14]

Risperidone	Costs	Orodispersible tablets
500 microgram	£1.13	£28.36
1mg	£1.12	£21.07
2mg	£0.66	£38.77
3mg	£0.83	£33.50
4mg	£0.92	£37.95
6mg	£3.85	-

Summary

- Appropriately prescribed, generically available atypical antipsychotics can release significant savings across the NHS. Simpler switches include changes from a brand to equivalent generic product or formulation switches for equivalent products.
- Commissioners and clinicians should agree local first line formulary choices which allow a range of products to be available for patient choice, based on side effect profile, efficacy and cost.

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Information compiled by Anita Hunjan, PrescQIPP Programme, July 2016 and reviewed by Katie Taylor, Senior Medicines Evidence Reviewer, August 2016.

Non-subscriber publication December 2016.

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