Addendum to the Evidence Review Group Report on Aripiprazole for the treatment of schizophrenia in adolescents (aged 15-17 years)

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Introduction

SHTAC were requested to provide additional analyses for the STA of aripiprazole for the treatment of schizophrenia in adolescents (aged 15-17 years). This addendum sets out to address the following questions:

1. What are the unit costs for risperidone and what are the likely daily costs for prescribing risperidone for adolescent schizophrenia?
2. Can an indication of the cost effectiveness of the first-line aripiprazole strategy compared with a first-line risperidone strategy be provided using the estimated costs for risperidone (for adolescent schizophrenia) and the manufacturer's economic model?

These issues were identified as important by NICE as risperidone is generally reported as the current standard first line treatment in adolescent schizophrenia, while the manufacturer's economic model includes olanzapine as the main comparator (due to inadequacies in the evidence base, discussed in the MS and the ERG report). Other comparators in the NICE scope were not modelled here. A limitation of this modelling is that data on risperidone is from one RCT only, not based on evidence from a systematic review.

1. To answer the first question, cost and packaging information from the BNF were used, along with the reported dosage from a published RCT using risperidone in adolescent schizophrenia (by Haas and colleagues[1]).

2. Two analyses were conducted to provide an indication of the cost effectiveness of first-line aripiprazole, relative to first-line risperidone. In both analyses the first-line aripiprazole strategy consisted of aripiprazole followed [on treatment discontinuation in the first cycle (due to adverse events, lack of efficacy or due to other causes) or on relapse in subsequent cycles] by risperidone, with clozapine reserved as a rescue medication. The first-line risperidone strategy consisted of risperidone followed [on treatment discontinuation in the first cycle (due to adverse events, lack of efficacy or due to other causes) or on relapse in subsequent cycles] by aripiprazole, with clozapine reserved as a rescue medication.

- 2a) In the first analysis, costs for olanzapine (in the manufacturer's economic model) were replaced with costs for risperidone. No other changes were made to the input data in the manufacturer's economic model.

- 2b) In the second analysis, odds ratios (ORs) for risperidone relative to aripiprazole, were estimated using an adjusted indirect comparison and included in the manufacturer's model. As noted, no additional searches were conducted. The analyses were performed using the limited data that had already been identified in the MS and therefore need to be interpreted with caution.

Key caveats on the adjusted indirect comparison and analyses presented in this addendum are:

- The evidence base for risperidone is very limited. It is not based on a systematic review, but on a single RCT.
- The RCT reported by Haas and colleagues[1] (for risperidone) is not a placebo-controlled trial, but compares the standard dose of risperidone with a "sub-therapeutic" (but not proven ineffective) dose.
- The duration of the trial reported by Haas and colleagues[1] is longer (8 weeks) than the trial for aripiprazole (6 weeks).
- There has been no assessment of similarities between studies.

Question 1 - Estimating the cost per day and cost per cycle for risperidone

Costs for risperidone were taken from the current BNF (No. 59, March 2010[2]) and were confirmed using the current BNF for children.[3] BNF for Children gives a dose range of 4-6mg per day for acute and chronic psychoses in children aged 12 to 18 years (stating additionally that risperidone is not licensed for use in children under 15 years for psychoses). However there is no dosing advice specific to adolescent schizophrenia. The median dose in the RCT reported by Haas and colleagues[1] was 4mg per day, using risperidone oral solution. Risperidone (generic) is available in 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg tablets, as 0.5mg, 1mg and 2mg orodispersible tablets and also a liquid (at concentration of 1mg/mL). Table 1 reports unit costs of risperidone (dosage, packet size, cost per packet and cost per milligram) and estimates of daily and cycle costs (assuming a dose of 4mg per day and a 42-day cycle, as in the manufacturer's model). There is a wide range in cycle costs depending on the preferred mode of administration (from £3.17 to £30.45 for tablets, £99.90 to £110.34 for orodispersible tablets and £90.55 for liquid). Table 2 reports the equivalent costs for a proprietary preparation of risperidone.

All drugs included in treatment strategies in the MS were costed on the basis of being administered as tablets – for consistency the base case analysis including risperidone will be costed on the basis of being administered as tablets and will only consider options that will deliver the required daily dose exactly (1mg, 2mg and 4mg for tablets or 1mg and 2mg for orodispersible tablets). In the base case reported in the following section we adopt a daily cost of £0.725 for risperidone (non-proprietary, delivered as a 4mg tablet). A range of potential daily costs (from a low of £0.101 for 2 x 2mg tablets of risperidone [non-proprietary] daily to a high of £2.157 for a branded oral solution) will be considered in a scenario analysis.

Table 1 Risperidone unit costs, cost per day and cost per cycle (non-proprietary)

Mode of administration	Dose	Pack size	Cost (£)	Cost per mg (£)	Cost per day[a] (£)	Cost per cycle[b] (£)
Tablet	0.5mg	20 tablets	1.06	0.106	0.424	17.81
	1 mg	20 tablets	1.36	0.068	0.272	11.42
	1 mg	60 tablets	2.13	0.036	0.142	5.96
	2 mg	60 tablets	3.03	0.025	0.101	4.24
	3 mg	60 tablets	3.40	0.019	0.076	3.17
	4 mg	60 tablets	43.50	0.181	0.725	30.45
	6 mg	28 tablets	32.10	0.191	0.764	32.10
Orodispersible tablet	0.5 mg	28 tablets	8.37	0.598	2.391	100.44
	1 mg	28 tablets	18.39	0.657	2.627	110.34
	2 mg	28 tablets	33.30	0.595	2.379	99.90
Liquid	1 mg/mL	100 ml	53.90	0.539	2.156	90.55

[a] Daily dosage estimated at 4mg
[b] Assuming a daily dosage of 4mg and cycle length of 42 days (as in MS)

Table 2 Risperidone unit costs, cost per day and cost per cycle (branded)

Mode of administration	Dose	Pack size	Cost (£)	Cost per mg (£)	Cost per day[a] (£)	Cost per cycle[b] (£)
Tablet	0.5mg	20 tablets	6.78	0.678	2.712	113.90
	1 mg	20 tablets	11.16	0.558	2.232	93.74
	1 mg	60 tablets	33.48	0.558	2.232	93.74
	2 mg	60 tablets	66.01	1.100	2.200	92.41
	3 mg	60 tablets	97.07	1.618	2.157	90.60
	4 mg	60 tablets	128.14	2.136	2.136	89.70
	6 mg	28 tablets	90.60	3.236	2.157	90.60
Orodispersible tablet	0.5 mg	28 tablets	10.98	0.784	3.137	131.76
	1 mg	28 tablets	17.67	0.631	2.524	106.02
	2 mg	28 tablets	33.31	0.595	2.379	99.93
	3 mg	28 tablets	48.38	0.576	2.304	96.76
	4 mg	28 tablets	62.31	0.556	2.225	93.47
Liquid	1 mg/mL	100 ml	53.93	0.539	2.157	90.60

[a] Daily dosage estimated at 4mg
[b] Assuming a daily dosage of 4mg and cycle length of 42 days (as in MS)

Question 2a – replace olanzapine costs with risperidone costs in first-line aripiprazole and first-line olanzapine strategies

To provide an indication of the cost effectiveness of first-line aripiprazole compared with first-line risperidone, the unit costs of risperidone were substituted in place of olanzapine in the manufacturer's economic model. This change only applies to the main lines of treatment – patients who relapse still receive olanzapine at the higher dose of 15mg per day for the duration of their relapse, as assumed in the manufacturer's base case. Caveats to be borne in mind with this analysis are that:

o Clinical data applied for risperidone [discontinuation in first cycle of treatment (due to intolerable adverse effects, lack of efficacy and all other causes) and treatment-related adverse effects (weight gain, somnolence and use of benzodiazepines (as proxy for EPS))] were based on olanzapine;

o This analysis does not account for adverse effects that might be relevant for the comparison of aripiprazole with risperidone, such as dystonia, cardiac arrhythmias, prolactin and cholesterol increase (which are less frequent with aripiprazole), or tremor (more frequent with risperidone).[4]

Table 3 reports results of analyses replicating those in the MS and in the ERG report for first-line aripiprazole compared with first-line olanzapine, and new analyses comparing first-line aripiprazole with first-line risperidone.

Table 3 Comparison of cost effectiveness results for first-line aripiprazole compared with first-line olanzapine and compared with first-line risperidone, based on the MS base case and on ERG corrections to the MS base case. Inpatient cost per day = £534 (as in original submission)

| | MS base case | | | | ERG corrected[a] | | | |
| | compared with first-line olanzapine | | compared with first-line risperidone | | compared with first-line olanzapine | | compared with first-line risperidone | |
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	23,723	2.597	22,786	2.597	24,483	2.597	23,546	2.597
First-line comparator	23,792	2.593	22,394	2.593	24,456	2.593	23,058	2.593
Difference	-69.21	0.004	391.77	0.004	27.15	0.004	488.14	0.004
ICER (£ per QALY gained)	Dominant		89,899		6,231		112,012	
[a] in the original submission, while a utility effect of relapsing patients on first-line medication (in the second model cycle) was applied, no cost of managing these relapses was included. The ERG included these costs in their corrected analysis.								

There was an error in the MS relating to estimated inpatient cost per day (clarification was requested from manufacturer). Table 4 reports results of analysis replicating those in the

manufacturer's response to our request for clarification and updating the ERG corrected results for the MS error in inpatient cost per day.

Table 4 Comparison of cost effectiveness results for first-line aripiprazole compared with first-line olanzapine and compared with first-line risperidone, based on the MS base case and on ERG corrections to the MS base case. Inpatient cost per day = 513 (as in clarification)

| | MS base case | | | | ERG corrected[a] | | | |
| | compared with first-line olanzapine | | compared with first-line risperidone | | compared with first-line olanzapine | | compared with first-line risperidone | |
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,982	2.597	22,045	2.597	23,713	2.597	22,776	2.597
First-line comparator	23,054	2.593	21,656	2.593	23,693	2.593	22,295	2.593
Difference	-72.63	0.004	388.35	0.004	20.07	0.004	481.06	0.004
ICER(£ per QALY gained)	Dominant		89,114		4,607		110,388	

[a] in the original submission, while a utility effect of relapsing patients on first-line medication (in the second model cycle) was applied no cost of managing these relapses was included. The ERG included these costs in their corrected analysis.

There are no substantive differences between results in Table 3 and Table 4 – in all comparisons the cost difference is approximately £100 greater in the ERG corrected analyses compared with the results from the MS base case. In both Table 3 and Table 4 the MS base case reports first-line aripiprazole as dominating first line olanzapine, whereas the ERG corrected base case shows slightly higher costs for first-line aripiprazole compared with first line olanzapine. In contrast results based on both the MS base case assumptions and the ERG corrected analysis show first-line aripiprazole as more costly than first-line risperidone (with a cost difference between approximately £390 and £490). In all the analyses reported in Table 3 and Table 4 first-line aripiprazole is associated with high value ICERs compared with first-line risperidone (approximately £90,000 to £112,000 per QALY gained).

Table 5 reports total and incremental costs and QALYs along with ICERs for first-line aripiprazole compared with first-line risperidone, adopting low and high cost assumptions for risperidone as described earlier (see Table 1 and Table 2).

Table 5 Cost effectiveness of first-line aripiprazole compared with first-line risperidone. Adopting low and high cost assumptions for risperidone

	ERG corrected[a]			
	risperidone cost per day = £0.101		risperidone cost per day = £2.157	
	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,569	2.597	23,251	2.597
First-line risperidone	21,986	2.593	23,004	2.593
Difference	583.00	0.004	247.13	0.004
ICER (£ per QALY gained)	133,779		56,708	

[a] includes cost of managing relapses on first-line medication (in the second model cycle) and corrected inpatient cost per day

Table 6 and Table 7 report selected scenario analyses included in the ERG report, applied to the comparison of first-line aripiprazole with first-line risperidone. The manufacturer's base case assumed that the length of inpatient stay for relapsed patients was 42 days (1 cycle) without justifying this assumption. We did not identify any routine data sources for inpatient stay for relapsed adolescent patients with schizophrenia. However, clinical advice to the ERG suggested the length of stay assumed in the MS may be too low. For the scenario analysis we used an average length of stay from current HES data (107.7 days, note that these data are not reported for the adolescent age group alone). In the second scenario we applied the RR of relapse reported by Moeller and colleagues[5] rather than the value ▇▇▇▇▇▇ assumed by the manufacturer, derived as the ratio of the crude risks. In the third scenario we assumed that fewer adolescents who experience relapse would be admitted as in-patients. Clinical advice to the ERG suggested that this proportion may be lower in children and adolescents, than in adults (the base case value in the MS was based on a value adopted for the NICE guideline on adult schizophrenia[6]). For the final scenario we attempted to remove a possible double-counting of treatment costs, where relapsed patients accrue the full cycle cost of medication in the cycle in which they relapse and the full cycle costs of their next available line of medication in the following cycle, while also attracting the full cycle cost for management of relapse. The potential impact of this was explored by subtracting half the cycle cost for patients' current medication in the cycle in which they experience relapse, and also half the cycle cost of their next available line of medication in the cycle following relapse.

In the first and second scenarios (longer inpatient length of stay for relapsed patients and using the reported RR of relapse) the difference in cost between first-line aripiprazole and first-line risperidone increased by around a half, while the QALY gain reduced very slightly in the second scenario (from 0.0044 to 0.0040), resulting in ICERs around £170,000 per

QALY gained. Reducing the proportion of relapsed patients who were expected to be treated as inpatients resulted in a slight reduction in the cost between first-line aripiprazole and first-line risperidone, however the ICER remained high (approximately £97,000 per QALY gained) – see Table 6. Table 7 reports the cumulative effect of these changes, with the ICER rising from £110,388 to £244,035 per QALY gained.

Table 6 Selected scenario analyses applied to comparison with first-line risperidone

	ERG corrected[a]		LOS = 107.7		RR relapse = 0.92		% IP = 50		Adjust drug cost for relapse	
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,776	2.597	52,107	2.597	22,272	2.598	16,403	2.597	22,670	2.597
First-line risperidone	22,295	2.593	51,357	2.593	21,580	2.594	15,981	2.593	22,146	2.593
Difference	481.06	0.004	750.69	0.004	692.00	0.004	422.48	0.004	523.34	0.004
ICER (£ per QALY gained)	110,388		172,260		172,864		96,945		120,091	

[a] includes cost of managing relapses on first-line medication (in the second model cycle) and corrected inpatient cost per day

Table 7 Repeat above but cumulative

	ERG corrected[a]		LOS = 107.7		RR relapse = 0.92		% IP = 50		Adjust drug cost for relapse	
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,776	2.597	52,107	2.597	50,857	2.598	34,551	2.598	34,448	2.598
First-line risperidone	22,295	2.593	51,357	2.593	49,597	2.594	33,615	2.594	33,471	2.594
Difference	481.06	0.004	750.69	0.004	1,260.24	0.004	936.10	0.004	976.91	0.004
ICER (£ per QALY gained)	110,388		172,260		314,810		233,840		244,035	

[a] includes cost of managing relapses on first-line medication (in the second model cycle) and corrected inpatient cost per day

Question 2b – replace olanzapine costs with risperidone costs and update odds ratios for discontinuations and adverse effects using available (less valid) data

The previous analysis did not use any clinical data specific to risperidone, and implicitly assumes that ORs derived for olanzapine (relative to aripiprazole) can be applied to risperidone. To examine the impact of applying ORs derived from an alternative data source, an adjusted indirect comparison was conducted using data from the RCT reported by Haas and colleagues[1] to estimate the ORs for discontinuation (due to adverse events, lack of efficacy and other reasons) and for treatment-related adverse effects (weight gain, somnolence and EPS). Caveats to be borne in mind with this analysis are that:

o The RCT reported by Haas and colleagues[1] (for risperidone) is not a placebo-controlled trial, but compares the standard dose of risperidone with a "subtherapeutic" (but not proven ineffective) dose;

o The duration of the trial reported by Haas and colleagues[1] is longer (8 weeks) than the trial for aripiprazole (6 weeks);

o The analysis does not account for adverse effects that might be relevant for the comparison of aripiprazole with risperidone, such as dystonia, cardiac arrhythmias, prolactin and cholesterol increase, or tremor;[4]

o Assumptions have been made from the available evidence around values for weight gain and EPS.

Table 8 reports the input data for aripiprazole used in the adjusted indirect comparison (taken from MS). The majority of these data were taken from the MS (Table 21, page 53). Data on EPS were taken from Findling and colleagues.[7]

Table 8 Input data for aripiprazole in adjusted indirect comparison

	Aripiprazole			Placebo			OR	SE	95%CI
	Events	Non Events	N	Events	Non Events	N			
Withdrawal (AE)	7	93	100	2	98	100	3.69	0.8147	0.75, 18.21
Withdrawal (LoE)	■	■	100	■	■	100	5.21	1.1048	0.60, 45.43
Withdrawal (other)	■	■	100	■	■	100	0.55	0.6434	0.16, 1.95
Weight gain	■	■	84	■	■	89	10.01	1.4986	0.53, 188.75
Somnolence	11	89	100	6	94	100	1.94	0.5286	0.69, 5.46
EPS[a]	13	87	100	5	95	100	2.84	0.5468	0.97, 8.29

[a] EPS events were based on symptoms not on use of benzodiazepines (used as a proxy for EPS in the MS)

Table 9 reports the input data for risperidone used in the adjusted indirect comparison (taken from the RCT reported by Haas and colleagues[1]). Note that the comparator group in this trial was low-dose risperidone, not placebo.

Table 9 Input data for risperidone in adjusted indirect comparison

	Risperidone (standard)			Risperidone (low dose)			OR	SE	95%CI
	Events	Non Events	N	Events	Non Events	N			
Withdrawal (AE)	5	120	125	6	126	132	0.88	0.6188	0.26, 2.94
Withdrawal (LoE)	19	106	125	26	106	132	0.73	0.3316	0.38, 1.40
Withdrawal (other)	11	114	125	18	114	132	0.61	0.4050	0.28, 1.35
Weight gain[a]	22	103	125	7	125	132	3.81	0.4539	1.57, 9.28
Somnolence	33	92	125	11	121	132	3.95	0.3746	1.89, 8.22
EPS[b]	41	84	125	13	119	132	4.47	0.3487	2.26, 8.85

[a] the OR calculated for weight gain is based on figures reported in the trial publication for patients [who] "experienced weight gain as an adverse event". No further details of this categorisation are given. This contrasts with the analysis presented in the MS, for aripiprazole, which defined significant weight gain as being an increase of greater than or equal to 7% over baseline.
[b] EPS events were based on symptoms not on the use of benzodiazepines (used as a proxy for EPS in the MS)

Table 10 reports the ORs for risperidone compared with aripiprazole, estimated in the adjusted indirect comparison, which suggest that risperidone is favoured over aripiprazole in terms of withdrawal (due to adverse events and lack of efficacy) though this is not statistically significant at 5% level. The ORs also suggest that risperidone is favoured over aripiprazole in terms of weight gain as a treatment-related adverse effect. In contrast, aripiprazole is favoured over risperidone for somnolence and EPS.

Table 10 Odds ratios of risperidone versus aripiprazole estimated in the adjusted indirect comparison

	OR	SE	95%CI
Withdrawal (AE)	0.237	1.0231	0.032, 1.762
Withdrawal (LoE)	0.140	1.1535	0.015, 1.345
Withdrawal (other)	1.104	0.7603	0.249, 4.899
Weight gain	0.381	1.5658	0.018, 8.203
Somnolence	2.038	0.6479	0.572, 7.255
EPS	1.574	0.6485	0.441, 5.610

Table 11 reports results of analyses replicating those in the MS and in the ERG report for first-line aripiprazole compared with first-line olanzapine and compared with first-line risperidone, including the ORs estimated in the adjusted indirect comparison (reported in Table 10). The overall effect of the updated assumptions for the ORs for discontinuation and

adverse effects has made the first-line aripiprazole strategy less effective than the first-line risperidone strategy. Taking this in conjunction with the lower cost of the first-line risperidone strategy means that the first-line aripiprazole strategy is dominated.

Table 11 Comparison of cost effectiveness results for first-line aripiprazole compared with first-line olanzapine and compared with first-line risperidone, based on the MS base case and on ERG corrections to the MS base case. Inpatient cost per day = £534 (as in original submission)

| | MS base case | | | | ERG corrected[a] | | | |
| | compared with first-line olanzapine | | compared with first-line risperidone | | compared with first-line olanzapine | | compared with first-line risperidone | |
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	23,723	2.597	22,576	2.601	24,483	2.597	23,336	2.601
First-line comparator	23,792	2.593	21,814	2.604	24,456	2.593	22,629	2.604
Difference	-69.21	0.004	762.07	-0.003	27.15	0.004	707.10	-0.003
ICER (£ per QALY gained)	Dominant		Dominated		6,231		Dominated	

[a] includes cost of managing relapses on first-line medication

There was an error in the MS relating to estimated inpatient cost per day (clarification was requested from manufacturer). Table 12 reports results of analysis replicating those in the manufacturer's response to our request for clarification and updating the ERG corrected results for the MS error in inpatient cost per day.

Table 12 Comparison of cost effectiveness results for first-line aripiprazole compared with first-line olanzapine and compared with first-line risperidone, based on the MS base case and on ERG corrections to the MS base case. Inpatient cost per day = 513 (as in clarification)

| | MS base case | | | | ERG corrected[a] | | | |
| | compared with first-line olanzapine | | compared with first-line risperidone | | compared with first-line olanzapine | | compared with first-line risperidone | |
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,982	2.597	21,835	2.601	23,713	2.597	22,566	2.601
First-line comparator	23,054	2.593	21,078	2.604	23,693	2.593	21,861	2.604
Difference	-72.63	0.004	757.42	-0.003	20.07	0.004	704.54	-0.003
ICER (£ per QALY gained)	Dominant		Dominated		4,607		Dominated	

[a] includes cost of managing relapses on first-line medication

Table 13 reports total and incremental costs and QALYs along with ICERs for first-line aripiprazole compared with first-line risperidone, adopting low and high cost assumptions for risperidone as described earlier (see Table 1 and Table 2).

Table 13 Cost effectiveness of first-line aripiprazole compared with first-line risperidone. Adopting low and high cost assumptions for risperidone

	ERG corrected[a]			
	risperidone cost per day = £0.101		risperidone cost per day = £2.157	
	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	£22,349	2.601	£23,065	2.601
First-line risperidone	£21,488	2.604	£22,719	2.604
Difference	£860.91	-0.003	£345.68	-0.003
ICER (£ per QALY gained)	Dominated		Dominated	
[a] includes cost of managing relapses on first-line medication (in the second model cycle) and corrected inpatient cost per day				

Table 14 and Table 15 report selected scenario analyses included in the ERG report, applied to the comparison of first-line aripiprazole with first-line risperidone. First-line aripiprazole is dominated by first-line risperidone in each of the scenario analyses.

Table 14 Selected scenario analyses applied to comparison with first-line risperidone

	ERG corrected[a]		LOS = 107.7		RR relapse = 0.92		% IP = 50		Adjust drug cost for relapse	
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,566	2.601	51,897	2.601	22,057	2.602	16,193	2.601	22,461	2.601
First-line risperidone	21,861	2.604	51,095	2.604	21,082	2.605	15,510	2.604	21,734	2.604
Difference	704.54	-0.003	802.12	-0.003	975.95	-0.003	683.34	-0.003	726.96	-0.003
ICER (£ per QALY gained)	Dominated		Dominated		Dominated		Dominated		Dominated	
[a] includes cost of managing relapses on first-line medication										

Table 15 Repeat above but cumulative

	ERG corrected[a]		LOS = 107.7		RR relapse = 0.92		% IP = 50		Adjust drug cost for relapse	
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs
First-line aripiprazole	22,566	2.601	51,897	2.601	50,643	2.602	34,337	2.602	34,235	2.602
First-line risperidone	21,861	2.604	51,095	2.604	49,194	2.605	33,158	2.605	33,035	2.605
Difference	704.54	-0.003	802.12	-0.003	1,448.56	-0.003	1,178.97	-0.003	1,199.67	-0.003
ICER (£ per QALY gained)	Dominated		Dominated		Dominated		Dominated		Dominated	
[a] includes cost of managing relapses on first-line medication										

Summary

First-line aripiprazole is a less cost effective option when compared with first-line risperidone, rather than with first-line olanzapine. However the analyses presented here need to be interpreted with caution.

The first approach to estimating the cost effectiveness of first-line aripiprazole, compared with first-line risperidone, was based solely on replacing olanzapine costs in the manufacturer's economic model with costs for risperidone. The clinical data relating to early discontinuations with first-line risperidone were based on ORs estimated for olanzapine relative to aripiprazole.

In the second approach to estimating the cost effectiveness of analysis first-line aripiprazole, compared with first-line risperidone, ORs relating to early discontinuations with risperidone (based on an adjusted indirect comparison) were applied in the model. It should be noted that, while the RCT of aripiprazole (reported by Findling and colleagues[7]) was placebo-controlled, the RCT of risperidone (reported by Haas and colleagues[1]) compared standard-dose with a "sub-therapeutic" (but not proven ineffective) dose. The occurrence of treatment discontinuation associated with risperidone may be under-estimated, by comparing standard-dose with an active (if "sub-therapeutic") comparator. Hence the ORs derived in the adjusted indirect comparison may be biased against aripiprazole.

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