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Overview of Atypical Antipsychotic Monotherapy for Schizophrenia: Clinical Review and Economic Evaluation of First Year of Treatment



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Canadian Agency for Drugs and Technologies in Health

**Overview of Atypical Antipsychotic Monotherapy
for Schizophrenia: Clinical Review and
Economic Evaluation of First Year of Treatment**

September 2007

We thank Suzanne Morphet for her assistance in creating this overview from a longer report authored by Farahati, *et al.*

This Overview is based on a technology report commissioned by CADTH: Farahati F, Boucher M, Moulton K, Williams R, Herrmann N, Silverman M, Skidmore B. *Atypical antipsychotic monotherapy for schizophrenia: clinical review and economic evaluation of first year of treatment*. [Technology report number 91]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007

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Atypical Antipsychotic Monotherapy for Schizophrenia: Clinical Review and Economic Evaluation of First Year of Treatment

Technology and Condition

Widely available atypical antipsychotics (AAPs) (risperidone, olanzapine, quetiapine, and clozapine) for treatment of schizophrenia.

Issue

Prescription medication costs for schizophrenia – driven by the use of AAPs – increased from C\$48.13 million in 1996 to C\$150 million in 2004. Health funders and practitioners need to know the comparative costs and benefits of the four agents widely used for maintenance therapy of patients with schizophrenia.

Methods and Results

We appraised and summarized the findings from a drug class review on AAPs. A systematic review of economic evaluations was conducted, with a cost analysis from the perspective of a Canadian third-party payer. A deterministic decision tree followed a theoretical cohort of recently diagnosed and already-treated patients for 12 months, using observational data from a Canadian setting, and results from the clinical review. The model suggests that starting with risperidone, olanzapine, or quetiapine will cost the health care system \$17,950, \$18,327, and \$19,695 for the first 12 months respectively. Risperidone remained the least costly under different scenarios. Funding generic risperidone also represented the smallest fiscal impact to drug plan budgets.

Implications for Decision Making

- **Differences exist among atypical antipsychotics.** The available evidence suggests that, compared with risperidone, olanzapine is associated with a lower risk of relapse and of treatment discontinuation, but is less well tolerated. Evidence also shows that clozapine use reduces suicide risk in high-risk patients, compared with olanzapine.
- **Costs to the health care system do not reflect differences in utilization costs.** Generic and brand-name olanzapine will require a larger investment by drug plans than quetiapine and risperidone. These costs are offset by reduced downstream costs from hospitalization, the largest cost component for treating patients with schizophrenia.
- **Decisions should be revisited.** The lack of high-quality evidence to inform first-line therapy reimbursement decisions suggests that additional analysis should be undertaken when comparative effectiveness studies are available. The costs associated with polytherapy, long-term treatment, and the role of traditional antipsychotics should be considered.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Farahati F, Boucher M, Moulton K, Williams R, Herrmann N, Silverman M, Skidmore B. *Atypical antipsychotic monotherapy for schizophrenia: clinical review and economic evaluation of first year of treatment.*

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CADTH is an independent, not-for-profit organization that supports informed health care decision making by providing unbiased, reliable information about health technologies.

1 Introduction

About 0.6% of Canadians will develop schizophrenia at a point in their lives,¹ usually starting in their late teens or early 20s.² In 2005, this totalled 198,803 individuals. People with this mental illness are significantly more likely to be suicidal and violent, and engage in substance abuse. They are more likely to experience homelessness, unemployment, medical illness, and victimization. Their life expectancy is significantly lower than average,¹ and the risk of suicide is 15 to 25 times higher than the average rate of approximately 0.5% to 1% in the general population.³⁻⁷

In addition to impairing an individual's ability to function over the long term, schizophrenia presents high costs to society. In 2004, the disease triggered direct costs of C\$2.02 million for hospitalizations, drugs, professional billings, residential-care facilities, and incarcerations.^{8,9} Even though the incidence of schizophrenia has stayed steady, the total economic cost – including indirect costs such as lost productivity – increased between 1996 and 2004, from about C\$2.35 billion to about C\$6.85 billion.^{8,9} The cost of prescription drugs for schizophrenia during this period jumped from C\$48.13 million to C\$150 million. Prescription costs accounted for 4.3% to 7.4% of the total direct health-care and non-health-care costs.^{8,9}

Physicians typically prescribe an antipsychotic to treat schizophrenia. Increasingly, they choose a newer atypical antipsychotic (AAPs) partly because of the perceived lower risk of short- and long-term extrapyramidal symptoms (EPS).¹ There is a concern, however, that the long-term use of AAPs by patients with schizophrenia is associated with diabetes mellitus (DM), weight gain, and increased cholesterol levels. Drug plan funders and practitioners would benefit from knowing the comparative costs and benefits of the AAPs.

In Canada, four AAPs have been approved for the maintenance treatment of schizophrenia: olanzapine (Zyprexa[®], Lilly),¹⁰ risperidone (Risperdal[®], Janssen Ortho and generics),¹¹ quetiapine (Seroquel[®], AstraZeneca),¹² and clozapine (Clozaril[®], Novartis Pharmaceuticals and generics).¹³ Because clozapine leads to a significantly increased risk of agranulocytosis and seizures, its use is restricted to patients who do not respond to other AAPs or traditional antipsychotics. Although aripiprazole is available through the Special Access Program, no Canadian jurisdiction reimburses patients for it, and it was excluded from our analysis.

Each province determines the formulary status of AAPs for its publicly funded drug plan. Although differences exist across Canada, risperidone is most commonly listed as a benefit without restrictions [i.e., full benefit, except the new injectable long-acting (L-A) form], followed by quetiapine. Three provinces list olanzapine and clozapine as full-benefit drugs; the other provinces limit their use.

We estimated the unit costs of AAPs in three ways:

- using brand-name prices from Saskatchewan Health 2007, with dosages from the Canadian Psychiatric Association (CPA) Practice Guidelines¹ for patients with schizophrenia and related disorders
- using generic prices and most common dosages for the treatment of patients with schizophrenia and related disorders, as described in the Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)¹⁴ (Table 1)
- using brand-name prices from publicly funded drug plans in Ontario, Saskatchewan, Prince Edward Island, and Newfoundland and Labrador, with dosages from the CPA (Table 6 in the technology report).

Table 1: Examples of unit costs and annual costs of AAPs available in Canada for treatment of schizophrenia

Generic Name	Trade Name	Unit Cost C\$	Annual Cost C\$ Canadian Guidelines Dosages	Annual Cost C\$ Most Common Dosages (CNOMSS)¹⁴
risperidone*	Risperdal 1 mg tablet	1.20	2 to 6 mg/day 876 to 2,628	4.2 mg/day 1,840
	Risperdal oral solution 1 mg/mL	1.38	1,007 to 3,022	2,116
	generic risperidone* 1 mg/mL oral solution	0.84	613 to 1,840	1,288
olanzapine*	Zyprexa (EDS) 5 mg tablet	3.67	10 to 20 mg/day 2,679 to 5,358	14.3 mg/day 3,831
	generic olanzapine 2.5 mg	1.18	1,723 to 3,446	2,464
quetiapine*	Seroquel 100 mg	1.43	600 mg/day 3,132	372.7 mg/day 1,945
clozapine*	Clozaril (EDS)100 mg	4.08	300 to 600 mg/day 4,468 to 8,935	383.5 mg/day 5,711
	generic clozapine(EDS) 100 mg tablet	2.87	3,143 to 6,285	4,017

EDS=Exception Drug Status; mg=milligram; mL=millilitre; *Saskatchewan Health 2007.¹⁵

2 Objectives

This report has three objectives:

- to compare the clinical effectiveness of clozapine, olanzapine, quetiapine, and risperidone (including oral and L-A injectable forms) for the maintenance treatment of schizophrenia and related psychoses
- to evaluate the comparative costs (including clinical benefits and harms) associated with the use of these AAPs for these disorders during the first 12 months after the start of treatment
- to estimate the impact of the use of these drugs for these disorders on Canada's publicly funded health-care system.

3 Clinical Review Methods

Our main source of clinical information was the Drug Effectiveness Review Project (DERP) published in April 2006 with the participation of the Canadian Agency for Drugs and Technologies in Health. The DERP, managed by the Centre for Evidence-based Policy at the Oregon Health & Science University, reviews large drug classes using a systematic approach. For AAPs, DERP searched three electronic databases until the first quarter of 2005: the Cochrane Central Register of Controlled Trials, Medline, and PsycINFO. Reference lists were searched, as were medical and statistical reviews and pharmaceutical manufacturers' dossiers. A meta-analysis was conducted when data were suitable for statistical pooling.

All studies that met the pre-determined inclusion criteria were described in the DERP report. Only studies that were rated good or fair were analyzed. The quality of the DERP report was determined using the annotated Oxman-Guyatt quality checklist for review articles.¹⁶ The quality was good, and

we gave an overall rating of 5 out of 7, because the review is likely to have minor flaws. The only potential concern was the possibility of selection bias, because the DERP report does not state that two reviewers worked independently at selecting studies. There was also no statement regarding how the reviewers resolved disagreements.

The DERP reviewers gave the highest weighting to head-to-head randomized controlled trials (RCTs) with effectiveness outcomes, followed by head-to-head trials with efficacy outcomes, then observational studies. Indirect comparisons were only used when direct evidence was unavailable. The inclusion criteria for effectiveness and efficacy outcomes were mortality (prevention of suicide), symptom response (e.g., mental state), functional capacity (e.g., employment), and hospitalization. Tolerability and harm outcomes included overall adverse events (AEs), withdrawals due to AEs, tolerability (e.g., weight gain), and long-term harms and serious AEs.

4 Results

Sixty-four head-to-head RCTs on schizophrenia met the inclusion criteria and provided most of the information on clinical benefits, tolerability, and short-term AEs. For the assessment of long-term serious harms, 44 observational studies were analyzed, including some poor-quality studies. All studies included patients with schizophrenia, but a few included patients with conditions such as bipolar disorder.

The largest effectiveness trial in the DERP review was the 18-month Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which looked at 1,493 patients with established schizophrenia who were not treatment-resistant.¹⁷ Of these, 336 were on olanzapine, 341 were on risperidone, and 337 were on quetiapine, with doses in the mid-range. CATIE showed that olanzapine is more effective than quetiapine on five measures, and superior to quetiapine and risperidone on six measures.

The systematic review of clinical effectiveness showed that differences exist among AAPs. Clozapine reduces suicidality in high-risk patients more than olanzapine. The maintenance use of olanzapine has a lower risk of treatment discontinuation and longer time to treatment discontinuation than risperidone or quetiapine. It has less risk of short- to medium-term relapse compared with risperidone (although this evidence is of lower strength and results for negative symptoms are inconsistent). On the plus side for risperidone, hospitalized patients experience a shorter length of stay, with faster onset of efficacy and lower rates of treatment discontinuation due to lack of efficacy, compared to olanzapine.

Olanzapine is associated with a higher risk of treatment discontinuation due to AEs than risperidone. The risk of weight gain ($\geq 7\%$ from baseline) is greater with olanzapine than with the other AAPs. Olanzapine leads to a greater risk of new-onset DM than risperidone. The risk of EPS is higher with risperidone than quetiapine, especially at higher doses (>5 mg/day). The risks of other AEs (hypersalivation, dizziness, somnolence, and constipation) are higher with olanzapine than risperidone, while quetiapine causes more somnolence, dizziness, and dry mouth than risperidone.

5 Economic Analysis and Systematic Review

Methods

We identified published economic literature by searching MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, and PsycINFO on May 18, 2006 without restrictions. Updates were received monthly. We searched The Cochrane Library 2006, Issue 2 and the May 2006 Health Economic Evaluations Database (HEED), with new issues of both as they arrived. We found grey literature by searching health technology assessment web sites and databases, and by using Internet search engines. We manually searched the bibliographies and abstracts of selected publications, and contacted manufacturers of AAPs and experts.

We included full and partial economic evaluations with no time or geographic restrictions. Two reviewers independently selected papers and resolved differences by consensus. A third reviewer acted as a referee, when necessary. One reviewer extracted data and the second checked it. We used the Drummond *et al.*¹⁸ checklist to assess cost and consequences analyses (CCAs) and cost-effectiveness analyses (CEAs) for quality. We did not do a summary estimate. Instead, we synthesized the available evidence descriptively.

Results

Of the 1,461 citations from our electronic search, 34 met the inclusion criteria, including four from Canada. All studies included patients with schizophrenia or schizoaffective and schizophreniform disorders. We included all pharmaco-economic studies that focused on one of the four AAPs of interest. Seven studies were CCAs, 13 were CEAs, and 14 were full or partial cost-analyses. All but two studies^{14,19} took the health care payer's perspective, and one²⁰ used the health-care payer's and societal perspectives. The study populations were adult in-patients or outpatients. Overall, the studies were fair to good in methods and analyses, and poor in underlying assumptions, generalizability of patient populations, and study design. The 12-month studies were too short to account for the cost of all consequences, so discounting was not applied.

Of the 34 studies, six described olanzapine as optimal, seven cited risperidone, and four reported equal or similar cost-effectiveness between the two. Most studies found that hospitalization is the biggest cost, accounting for a third to half of the total annual cost of treating patients (e.g., CATIE,²¹ CNOMSS,¹⁴ Edwards *et al.*,²² Tunis *et al.*,²³ Vera-Llonch *et al.*²⁴). Medications were the second largest cost, accounting for 60% of the total cost for patients using olanzapine, 30% for quetiapine, 40% for risperidone, and 50% for clozapine (Table 4 of the technology report) without considering group-home care costs.

6 Economic Evaluation

Methods

We built a decision tree to project the first 12-month costs after the start of treatment for each of the four AAPs, accounting for the likelihood of switching from one AAP to another, as patients progress from first-line to second-line and third-line therapy options. The model considered the time to

encounter these events and length of hospital stay. The decision-tree model was built using DATA 3.0.1 software (TreeAge Pro 2005).

This model accounts for the probability of patients discontinuing treatment or being hospitalized because of disease exacerbation or AEs. We used direct costs only, such as those for medications and hospitalization. For the base case, we calculated medication costs by applying the minimum, maximum, and average dosages recommended by the Canadian Psychiatric Association¹ to unit costs from four publicly funded drugs plans in Canada. For the sensitivity analyses, the results were examined using generic and brand-name prices, and the most commonly used dosages in Canada (CNOMSS). A complementary literature search found a follow-up to CATIE.²⁵ Our perspective was that of Medicare, the publicly funded payer.

Based on the clinical and economic studies (described in the technology report), discontinuation rates for any reasons, relapse rates, and length of hospital stay are the most important effectiveness outcomes in these disorders. Our model considered recently diagnosed patients and those previously treated with a traditional antipsychotic. Risperidone, olanzapine, and quetiapine were considered to be first- and second-line treatment options. Clozapine was limited to third-line therapy. The duration for clozapine was estimated by subtracting the time remaining after first- and second-line therapies. This was 2.7 months after risperidone and olanzapine, 2.83 months after olanzapine and quetiapine, and 5.73 months after quetiapine and risperidone. Given the 12-month time horizon and insufficient evidence describing polypharmacy with AAPs, we assumed no treatment discontinuation with clozapine. We considered all costs including those of relapse and hospitalization in the form of lump-sum costs for clozapine. We selected those outcomes from the DERP review for which observed differences were clinically and statistically significant (as determined by DERP), and economically significant (as determined by author FF) (Table 2).

Results

First, we evaluated the mean first-year cost, accounting for the probability of all events (from Table 2), without considering the switch rates. Our decision tree model, which was more comprehensive and incorporated 294 scenarios based on the discontinuation rates and relapses from Table 2, suggests that the average treatment costs based on historical data vary. Risperidone is least costly, followed by olanzapine and quetiapine. In the base-case analysis, which used historical utilization and costs, these were \$17,950, \$18,327, and \$19,695 for risperidone, olanzapine, and quetiapine respectively.

Patients who stayed on their initial treatment had the lowest annual costs. About 18.8% of patients stayed on risperidone, 19.1% on olanzapine, and 16.8% on quetiapine as first- and second-line therapies. About 45.2% of patients ultimately switched to third-line treatment. Because clozapine was a third-line therapy only, we estimated its cost in the form of lump sums for the remainder of the 12-month period, based on discontinuation and relapse rates from DERP for the other first- and second-line AAPs. We conducted sensitivity analyses to see the effect on costs of varying daily doses, discontinuation and relapse rates, and number of days in group-home care. We determined that their impact is small; risperidone and olanzapine remained the least costly choices.

Table 2: Pharmacoeconomic parameters used in base case economic evaluation model				
Parameter	1st and 2nd Line Treatment Cost with Risperidone	1st and 2nd Line Treatment Cost with Olanzapine	1st and 2nd Line Treatment Cost with Quetiapine	3rd Line Treatment Cost with Clozapine
From DERP Systematic Review				
proportion of overall discontinuation rates in phase 1 (estimated for 12 months)	66%*	54%*	76%*	NA
relapse (proportion of patients hospitalized because of exacerbation over 18 months)	15%*	11%*	20%*	20.8%†
time (in months) to discontinuation (estimated for 12 months)	3.2*	6.1*	3.07*	NA
mean length of in-patient stay	43.02‡	48.26‡	48.26‡	48.26‡
EPS	22%**	16.2%**	13%**	13%**
From Studies Excluded in DERP				
proportion of patients with diabetes mellitus (DM)	0.05%††	0.63%††	0.80%††	2.03%††
proportion of reasons for discontinuation from phase 1: due to inadequate therapeutic effects	90%‡‡	90%‡‡	80%‡‡	NA
proportion of reasons for discontinuation from phase 1: due to unacceptable side effects and patient's decision	10%‡‡	10%‡‡	20%‡‡	NA

NA=not applicable in decision tree; *CATIE I;¹⁷ †(InterSePT);²⁶ ‡pooled estimates of DERP^{15,27} in-patient RCTs; **risperidone from Zhong *et al.*,²⁸ olanzapine from Tran *et al.*,²⁹ quetiapine from Zhong *et al.*,²⁸ and clozapine from Azorin *et al.*,³⁰ ††Leslie *et al.*,³¹ ‡‡CATIE II.E.²⁵ From those who started with risperidone, olanzapine, or quetiapine and discontinued in 1st phase, 90% of risperidone and olanzapine groups and 80% of quetiapine group were assumed to discontinue because of inefficacy (and the rest because of side effects) thus were assigned to more effective AAPs (to less effective AAPs with fewer side effects) (see decision tree in Appendix 15 of technology report).

Limitations

The DERP report, our primary source of information, may have introduced some bias (we could not tell what steps had been taken to avoid bias) and it did not always provide high-quality evidence to inform our economic evaluation. Thus, we included two studies that were not identified from a systematic review: Leslie *et al.*³¹ for DM and CATIE II.E.²⁵ regarding “reasons for discontinuation” (Table 2). We invited input from reviewers and performed a sensitivity analysis to test the strength of our findings. Another possible limitation is that data from our model came largely from two trials^{17,26} and one Canadian observational study, CNOMSS,¹⁴ which recruited patients from the chronic schizophrenia population rather than newly diagnosed patients. These trials provided the best effectiveness data available.

Table 3: Estimated 1st-year costs to public drug plans and ministries of health of each AAP patient with schizophrenia (2005 base case analysis in C\$)

1st line AAPs	Cost for Publicly Funded AAPs	Cost to Ministries of Health
brand-name risperidone	minimum and maximum dosages from CPA ¹ 2 to 6 mg/day, 851 to 2,554	minimum and maximum dosages from CPA, 16,729 to 19,167
	common dosages from CNOMSS ¹⁴ 4.2 mg/day, 1,786	common dosages from CNOMSS, 17,774
generic risperidone	minimum and maximum dosages from CPA 2 to 6 mg/day, 613 to \$1,840	minimum and maximum dosages from CPA, 16,188 to 17,612
	common dosage from CNOMSS 4.2 mg/day, 1,288	common dosages from CNOMSS, 16,686
brand-name olanzapine	minimum and maximum dosages from CPA 10 to 20 mg/day, 2,854 to 5,709	minimum and maximum dosages from CPA, 16,936 to \$19,718
	common dosages from CNOMSS 14.3 mg/day, 4,082	common dosages from CNOMSS, 18,084
generic olanzapine	minimum and maximum dosages from CPA 10 to 20 mg/day, \$1,723 to \$3,446	minimum and maximum dosages from CPA, 16,096 to 17,688
	common dosages from CNOMSS 14.3 mg/day, 2,464	common dosages from CNOMSS, 16,655
brand-name quetiapine	minimum and maximum dosages from CPA 600 mg/day, 3,454	minimum and maximum dosages from CPA, 18,832 to 20,556
	common dosages from CNOMSS 372.7 mg/day, 2,177	common dosages from CNOMSS, 18,905
brand-name quetiapine but using generic clozapine in 3 rd line therapy	minimum and maximum dosages from CPA 600 mg/day, \$3,454	minimum and maximum dosages from CPA, 18,452 to 19,328
	common dosages from CNOMSS 372.7 mg/day, 2,177	common dosages from CNOMSS, 18,050

Low cost of brand-name AAPs based on publicly funded drug plan costs; AAPs=atypical antipsychotics; CNOMSS=Canadian National Outcomes Measurements Study in Schizophrenia; CPA = Canadian Psychiatric Association.

7 Health System Implications

The number of Canadians affected by schizophrenia is approximately 0.6% of the adult population.¹ In 2004, this number was 192,242. By 2011, it is expected to be 203,458.^{9,32} Our primary economic evaluation projected the cost of AAPs when patients use monotherapy, but it is estimated that 62% of patients are taking one AAP.¹⁴ Many use more than one treatment. No research evidence is available to accurately model the costs of polypharmacy. The number of prescriptions for AAPs increased from about 2.7 million in 2000 to 6.6 million in 2004 and to 7.2 million in 2005, with costs of \$260 million, \$531 million, and \$580 million respectively (IMS Health Canada, 2006). Risperidone was the most prescribed AAP but olanzapine accounted for the largest expenditures (IMS Health Canada, 2006). Provincial drug plans paid for more than 67% of AAP prescriptions in 2000 and 64% in 2004 (ratio of drug utilization data provided by the publicly funded drug plans of British Columbia, Saskatchewan, Manitoba, Ontario, New Brunswick, Prince Edward Island, and Newfoundland and Labrador; and IMS Health Canada, 2006). It is estimated that 76,282 patients with schizophrenia were covered by public plans in 2004.³²

Table 3 presents the budgetary impact of assigning one new patient to each AAP (or publicly funded brand name) and downstream AE management costs.

8 Conclusions

From a clinical effectiveness perspective, olanzapine and risperidone are superior to quetiapine. Compared with risperidone, olanzapine is associated with a lower risk of relapse and of treatment discontinuation for any reason. The risk of treatment discontinuation due to AEs is higher. Evidence shows that clozapine reduces suicide risk in high-risk patients, compared with olanzapine.

From an economic perspective, good-quality evidence does not exist for all comparisons. Furthermore, heterogeneity among study design, data analysis, methods, cost components, settings, and presentation of findings makes comparisons and generalizability of results challenging.

Our economic evaluation, which considered the total direct costs of treatment, suggests that risperidone and olanzapine have similar first-year costs. Both are less than quetiapine. The results (in magnitude of costs) were sensitive to variations in discontinuation rates for any reasons, relapse rates, dosages, group-home care, and associated costs of AAPs, but robust to the preferred choices of risperidone and olanzapine. We found that EPS and new cases of DM associated with AAPs do not lead to substantial cost implications because of their low incidence in the first year of treatment.

Our economic model suggests that switching patients between AAPs without considering the discontinuation and relapse rates will not be cost-saving. The largest cost component for treating patients with schizophrenia is hospitalization due to the exacerbation of psychotic symptoms, so minimizing hospitalization should result in cost savings.

Regarding budgetary impact, the least-cost choice, on average, for first-line AAP therapy would be generic risperidone. Assigning each new patient to generic risperidone would cost Canadian public plans about \$613 to \$1,840 per patient and ministries of health approximately \$16,188 to \$17,612 per patient, depending on the dose prescribed, type of costs (generic, brand-name, or publicly funded brand name), and downstream AE management costs.

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