ECONOMIC EVALUATION OF THE NPS MEDICINEWISE PROGRAM BALANCING BENEFITS AND HARMS OF ANTIPSYCHOTIC THERAPY

REPORT

2015

Independent, not-for-profit and evidence based, NPS MedicineWise enables better decisions about medicines and medical tests. We receive funding from the Australian Government Department of Health.

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LIST OF ABBREVIATIONS

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
BEACH	Bettering the evaluation and care of health
BPSD	Behavioural and psychological symptoms of dementia
CBA	Cost benefit analysis
CVA	Cerebrovascular accident
CVAE	Cerebrovascular Adverse Events
DSM	Diagnostic and Statistical Manual of Mental Disorders
GP	General practitioner
HP	Health professional
ICD	International Classification of Diseases
OR	Odds ratio
PBS	Pharmaceutical benefit scheme
QALY	Quality Adjusted Life Year
RCT	Randomized controlled trial

EXECUTIVE SUMMARY

The *balancing benefits and harms of antipsychotic therapy* program conducted by NPS MedicineWise, began in 2011 and aimed to improve the quality of life of people through safe and effective use of antipsychotic medication while balancing optimal disease management. Part of the program focussed on reducing antipsychotics inappropriately prescribed to elderly patients with dementia. The program focussed on atypical or second generation antipsychotics, including the medications risperidone, quetiapine and olanzapine. For the behavioural symptoms of dementia, the use of non-pharmacological approaches is recommended as first–line therapy.

This economic evaluation identifies the costs and benefits of the program in monetary terms. NPS MedicineWise expected a decrease in volume of atypical antipsychotics as well as a reduction in potential side effects from the medications (strokes, falls, gait disturbances and death) to be observed in people aged 70 years and over following the completion of the program.

This study consists of: two meta-analyses examining the risk of falls and stroke and cerebrovascular adverse events (CVAE) following use of atypical antipsychotic medication (quetaipine, risperidone and olanzapine) among dementia patients; an assessment of the effectiveness of the program using data from the 2011 NPS clinical audit, the general practitioner survey and an interrupted time series analysis of administrative data from the Australian Pharmaceutical Benefits Scheme (PBS); and a cost-benefit analysis.

The meta-analyses found that the risk of a fall event was not statistically significant although the odds ratio of a stroke event or CVAE occurring was 1.67 higher in atypical antipsychotic users compared to non-users. The assessment of the effectiveness of the program found that 41% of GPs in Australia participated in the program which resulted in a 7.3% reduction in modelled PBS prescription volume with an estimated savings of $4.27 million. It was estimated that $2,229,230 was saved for state hospitals giving a total saving for the health system of $6.5 million. It was determined that 177 strokes were averted due to the program. After assessing the cost of the program and the savings in terms of PBS and hospital savings and the quality of life gains, the cost to benefit ratio was 2.4. For every $1 invested in the NPS MedicineWise intervention on antipsychotic medication for dementia patients, $2.40 in benefits was generated. There was an estimated net benefit of about $3.8 million. More savings to the health care system may have been found if the model took into account: NPS recommendations for alternatives to treatment; deaths; falls, infectious diseases and MBS item costs.

Although this study had many limitations the findings do show that the NPS MedicineWise program had effective health outcomes and quality of life gains for dementia patients as well as savings for the health care system.

1.INTRODUCTION

The purpose of this study was to undertake an economic evaluation of the NPS MedicineWise program 'Balancing benefits and harms of antipsychotic therapy'. The program was a multi-faceted academic detailing program aimed at improving quality of life of adults through safe and effective use of antipsychotics when indicated, while balancing optimal disease management. A significant component of this program focussed on reducing antipsychotics inappropriately prescribed to elderly patients with dementia.

1.1 Objectives of this report

This report represents one part of the evaluation of the NPS MedicineWise program 'Balancing benefits and harms of antipsychotic therapy'.

The key objectives of the antipsychotic program evaluation are:

- To identify any short-term or intermediate improvements in awareness, knowledge, attitudes and prescribing behaviour of health professionals in line with key messages
- To assess the impact of NPS interventions on changes in GP behaviour for medicine prescribing and savings on the PBS and to the health care system

The evaluation of the first objective was conducted in 2013.This evaluation assesses the impact of the program in reducing the prescribing of atypical antipsychotics to people aged 70 years and over with dementia and the reduction of adverse events due to stroke.

1.2 Rationale for the program

The last 10 years have seen a significant increase in the number of subsidised prescriptions for antipsychotic medicines, with a total of 2,511,874 subsidised prescriptions dispensed in Australia in 2008-09. Australian statistics for the period 2006-10 indicate an average year-to-year growth in antipsychotic use of approximately 5% (1). In 2009 alone, the total cost of atypical antipsychotics to the Australian government was more than $370 million, with the top three prescribed antipsychotics being; olanzapine risperidone and quetiapine (2). Data collected as part of the Bettering the Evaluation and Care of Health (BEACH) report on general practice activity in Australia (2012-2013) showed that, for every 100 encounters with a GP in Australia, 13.1 are related to psychological issues (0.6 per 100 exclusively dementia related). Of the prescribed medications during GP encounters, antipsychotics scripts are reported to be 1.3% of all prescriptions with an antipsychotic being prescribed 1.1 times for every 100 encounters (2).

The three medications (risperidone, quetiapine and olanzapine) that were chosen to be the focus of the 2011 NPS MedicineWise program are known as atypical, or second generation antipsychotics. This means that such medications are less likely to cause movement disorders secondary to the extra pyramidal effects of antipsychotics in general. Research has shown however that the use of atypical antipsychotics is poorly tolerated for the treatment of behavioural disturbances of dementia with increased risk of cardiovascular events or infections (3). Of the three medicines, only risperidone is PBS listed for behavioural symptoms of dementia (4).

The use of antipsychotics for the management of behavioural and psychological symptoms of dementia (BPSD), particularly within older people in the aged care setting, has become widespread. The most common BPSD include psychosis, agitation, wandering, shouting, repeated questioning and

sleep disturbance (5).The limited benefits of antipsychotics in treating aggression and psychotic symptoms associated with BPSD appear to be largely outweighed by the serious adverse effects, including an increased risk of stroke and death (5). For the behavioural symptoms of dementia, the use of non-pharmacological approaches is recommended as first-line therapy (5).

1.3 Overview of the program

In August 2011, NPS MedicineWise launched an 18 month visiting program 'Balancing benefits and harms of antipsychotic therapy' following recommendations from the Safety and Quality Partnership Subcommittee as well as stakeholder feedback. The program covered BPSD as well as bipolar and schizophrenia. The bulk of the GP visits took place between August 2011 and June 2012. In addition, at the time of the program development, two key studies were published in Australia examining the use of atypical antipsychotics to manage behavioural disturbance in older adults (6,7). The aim of this program was to improve knowledge, attitudes and prescribing behaviour among health professionals in line with key messages. This was the second antipsychotics program implemented, with the first program (non-visiting) running from April 2007 to August 2009.

Key program objectives and messages

There were seven objectives for the 2011 program:

1. Improve knowledge and skill amongst health professionals (HPs) in identifying and managing underlying external factors that influence behavioural disturbances
2. Improve knowledge, attitudes and skills amongst HPs in identifying and advising patients/carers on implementing non drug therapies to manage BPSD and other causes of behavioural disturbances when appropriate
3. Improve knowledge and skills amongst HPs to initiate antipsychotics, when indicated, as a time limited trial with agreed plans on review and outcomes for patients with BPSD
4. Improve HP knowledge on the benefits and risks of prescribing antipsychotics to the elderly
5. Improve knowledge and skills amongst HPs in monitoring of patients prescribed an antipsychotic to ensure target behaviour improves and that adverse drug events are minimized
6. Improve knowledge and skills amongst HPs on trialling a withdrawal of antipsychotics in patients where there is no clear benefit (may be restricted to the elderly)
7. Improve HPs knowledge in counselling patients/carers on the importance of patient adherence to antipsychotic medicines

Associated with these objectives were the following messages:

- Assess benefits and harms of antipsychotic therapy
- Engage patients/carers in recognising and managing adverse effects
- Reinforce the importance of adherence to antipsychotics when prescribed
- Review ongoing need for antipsychotics for behavioural symptoms of dementia and trial withdrawal.

Expected outcomes of the NPS MedicineWise program

Based on the key messages and an understanding of current prescribing practice, it was expected that the reduction in antipsychotics usage for BPSD would be a more appropriate approach compared to current practice, in particular, in adults aged 65 years and over. Therefore, NPS MedicineWise expected a decrease in total volume of atypical antipsychotics and a reduced incidence of strokes and falls to be observed in older people (65 years and over) following the completion of the program.

1.4 Antipsychotics and unintended consequences

Antipsychotics and falls

Epidemiology

A report published by the Australian Institute of Health and Welfare (AIHW) in 2012 reports that falls were the major cause of hospitalised injury cases in Australian adults aged 65 years and over (76.5% of all major causes of hospitalisation). Fall related hospitalisations results in an average of 8 day hospital stays, with the length of stay increasing with age. Of all fall injury cases reported in the period 2011-2012, the majority (42.8%) were in patients aged 85 years and over. Fractures were the most common injury sustained following the fall (57% of all injuries), in particular, fractures of the hip/s and/or lower limbs (35-40% of all fractures) (8).

In June 2004 and May 2010, twenty-two educational modules were delivered to general practitioners by the Department of Veterans affairs with the aim of providing up to date medicines and health information for Australian veterans. One of these modules, delivered in September 2007, focussed specifically on the use of antipsychotics in dementia. This module was delivered after case series studies conducted by the program developers identified significantly increased risk of hip fractures secondary to a fall caused by the use of antipsychotics (9).

A Cochrane review published in 2006 identified a number of studies that examined the incidence of falls following use of Risperidone and Olanzapine for up to 13 weeks, with the odds ratios for a falls event ranging from 1.16 to 2.24 (10).

The mechanism of action of antipsychotic drugs and age related altered pharmacodynamics are contributing factors to the link between antipsychotic use and falls among the elderly. A paper by Trifiro et al explains this link further by highlighting that elderly adults may experience increased responsiveness to antipsychotics “due to impaired adaptive and homeostatic mechanisms and depletion of dopamine reserves” (11). This translates to increases in anticholinergic effects and extrapyramidal effects as well as increased risk of orthostatic hypotension and cerebrovascular events. Such risks are present even with the newer, second generation antipsychotics (11).

Economic impact

A report to NSW Health conducted in 2010 examined the costs associated with fall related injuries among older adults in NSW. The cost of fall related hospital admissions varied by place of residence with hospitalisation for those aged 65 years and over residing in the community costing a total of $407.26 million compared to $64.44 million for those living in residential aged care facilities. The highest average cost for fall-related care was hospital admissions at $14,454 followed by cases treated in emergency departments at $2,721 and then non-hospital treatments at $369. The average cost of fall-related care is higher for community-dwelling older people at $4722 compared to $1979 for those in residential care. (12).

Antipsychotic and strokes

Epidemiology

In the literature examining the relationship between antipsychotics and adverse events, often strokes are categorised under the broader category of cerebrovascular adverse events (CVAEs). CVAEs refers to both strokes and transient ischemic attacks (TIAs). During the period 2009-2010, a total of 26,035 adults aged 65 years and over were hospitalised for a stroke. Hospitalisations related to TIAs during this same period occurred in 11,318 adults aged 65 years and over. Following a stroke event, patients admitted to hospital may require acute treatment such as thrombolysis or a carotid endarterectomy. Post-acute treatment often involves rehabilitation with 88% of stroke survivors with disability living in households and the rest living in cared accommodation (13).

A meta-analysis conducted by Schneider et al in 2006 outlined the adverse effects of atypical antipsychotics when prescribed for dementia patients. Results from the study indicated that the event of a stroke (and other cerebrovascular adverse events) following use of these medications was 1.9% compared to 0.9% for patients with dementia not on atypical antipsychotics. This risk translated into an odds ratio (OR) of 2.13. Risperidone in particular was shown to have a significantly increased risk compared to other atypical antipsychotics with an OR of 3.43 (14). The risk of a stroke following use of antipsychotics has been previously shown to be present in patients both with and without dementia (15). A report commissioned by the Department of Health in the United Kingdom identified that for every 1000 elderly adults with dementia treated with atypical antipsychotics, a total of 18 additional cerebrovascular events would occur within 12 weeks (16).

A causal relationship between atypical antipsychotic use and cerebrovascular events has been attributed to not only the cardiovascular effects mentioned previously (namely orthostatic hypotension and cardiac arrhythmias) but also the thromboembolic effects of atypical antipsychotics (due to the presence of anticardiolipin antibodies) as well as sedation leading to potential dehydration and thus haemoconcentration (17). Trifiro et al identify that orthostatic hypotension is the most likely cause of cerebrovascular adverse events among elderly users of antipsychotics with a diagnosis of dementia due to antagonism at alpha-adrenergic receptors (11).

Economic impact

Strokes are a major burden on the Australian health system and this is particularly the case with adults aged 65 years and over. A report commissioned by the National Stroke Foundation found the total cost of stroke health expenditure for adults 65 years and over was $745 million in 2012, almost 85% of all stroke health expenditure in Australia (17). The rate of hospitalisation following a stroke is highest for those aged 70 years and over, which accounted for 66% of all stroke hospitalisations in 2007-2008 (19). Estimated expenditure per person for hospital-admitted patients for stroke increased sharply with age, as did expenditure per person for prescription pharmaceuticals. In 2009, 375,800 people survived stroke with 25,300 hospitalisations for stroke and 25,800 hospitalised for rehabilitation care in 2009/10 (19).

2.METHODOLOGICAL APPROACH

2.1 Overview of the analysis

A Cost Benefit Analysis (CBA) compares the costs and effects of an intervention expressed in monetary terms. The following elements are required for a CBA:

- The **cost** of the resources required to deliver the interventions
- The **effects** of the interventions on incidence of stroke/CVAE/fall, expressed in natural units
- The **benefits** of the interventions expressed as the monetary value of the effects generated by the interventions

Decision models were built to assess the costs and benefits of the intervention with a separate decision model for each outcome. The structure of the decision models are presented in Appendix 1.

Estimates of the following costs and benefits were included in the models:

- **Costs** – estimated annual cost of NPS MedicineWise delivering the intervention;
- **Effects** – the effect of the intervention on reducing strokes/CVAE/falls relative to antipsychotic drugs;
- **Benefits** – in terms of health care cost savings and the quality of life gained by reducing stroke and falls.

2.2 Data Collection

This study consisted of several phases:

Phase 1: A literature review was undertaken and data sourced from randomised controlled trials were extracted to perform two meta-analyses examining the costs and risk of fall and stroke (and cerebrovascular adverse events(CVAE)) following use of atypical antipsychotics (quetiapine, risperidone and olanzapine) among dementia patients. The literature review and meta-analyses identified data on:

- the probability that individuals living with dementia experienced a stroke when receiving antipsychotic drugs in comparison to no use
- the probability that individuals living with dementia experienced a fall when receiving antipsychotic drugs in comparison to no use
- The cost per stroke/CVAE/fall
- QALY gain due to an avoided stroke/CVAE/fall

A QALY is a standardised measure of health gain. Quality of life is measured on a scale between 0 (death) and 1 (perfect health). One year of perfect health is measured as 1 QALY. There is an accepted monetary value for QALYs that allows these effects to be expressed in monetary values (5).

Phase 2: The effectiveness of the antipsychotics program was assessed using data from the 2011 NPS clinical audit, a survey conducted with general practitioner as part of the program and an interrupted time series analyses of administrative data from the Australian Pharmaceutical Benefits Scheme (PBS).

Phase 3: An impact analysis was conducted to assess the impact of the program in reducing adverse events: stroke incidence and related hospitalisations due to changes in antipsychotics prescribing attributable to the program. This was performed by developing a decision tree using TreeAge Pro software. Data from phase 1 and 2 were used to develop the model.

Phase 4: The cost of the NPS MedicineWise program and a budget impact analysis was conducted to measure the financial consequences of the program on the health system.

2.3 Models and presentation of results

The models were estimated for the duration of the NPS MedicineWise program.

Two indicators are used for the results of the CBA:

- The **net benefit**, which is calculated as the difference between the benefits and the costs. Values higher than zero indicate that the benefits exceed the costs, and thus the intervention represents an efficient use of public resources
- The **benefit-cost ratio**, which is calculated as the ratio of benefits to costs. Values higher than one indicate that the benefits exceed the costs, and thus the intervention represents an efficient use of public resources

3.RESULTS

3.1 Literature Review and Meta-Analyses

A total of 36 falls related studies and 39 stroke/CVAE related studies were identified with only six and ten studies included respectively. Pooled results of falls data indicated that the odds ratio of a fall event associated with antipsychotic use was not statistically significant. The results of the stroke/CVAE related studies indicated that the odds ratio of a stroke event or CVAE occurring was 1.67 higher in atypical antipsychotic users compared to non-users (95% CI: 1.26-2.21)

A meta-analysis design was used to systematically assess and pool the results of the literature search conducted. This design was chosen as it is able to provide a precise estimate of the treatment effect of antipsychotic as sourced from multiple studies.

Data sources and search strategies

A comprehensive literature search was conducted using CINAHL complete, Cochrane Library and MEDLINE (2008-present) databases. Published data from the last fifteen years was searched using the key words outlined in Table 1. In addition, Government agency reports were searched from the ABS and AIHW website for population statistics and costs (explained further in Part 2).

Study selection and quality assessment

Studies were selected for inclusion if they were a cohort study (either retrospective or prospective) or randomized controlled trial (RCT) and provided raw data on the incidence of either falls or strokes (or cardiovascular adverse events). Data related to falls or stroke events in older adults with a diagnosis of dementia were included. If the study met these criteria, the paper was then assessed using the CASP critical appraisal tools for the relevant study design (either randomised controlled trials or cohort studies) (20).

Data analysis

Data were extracted from each of the included studies and entered into a study database using Revman Software version 5.3 (21). This software was used to calculate pooled results grouped according to stroke and falls data. Evidence of heterogeneity was defined using a p-level of 0.10 and/or an I^2 value greater than 50% (22) and if heterogeneity was present a random-effects model was used. Studies were analysed separately by study design if there was evidence of heterogeneity when mixed study designs were pooled.

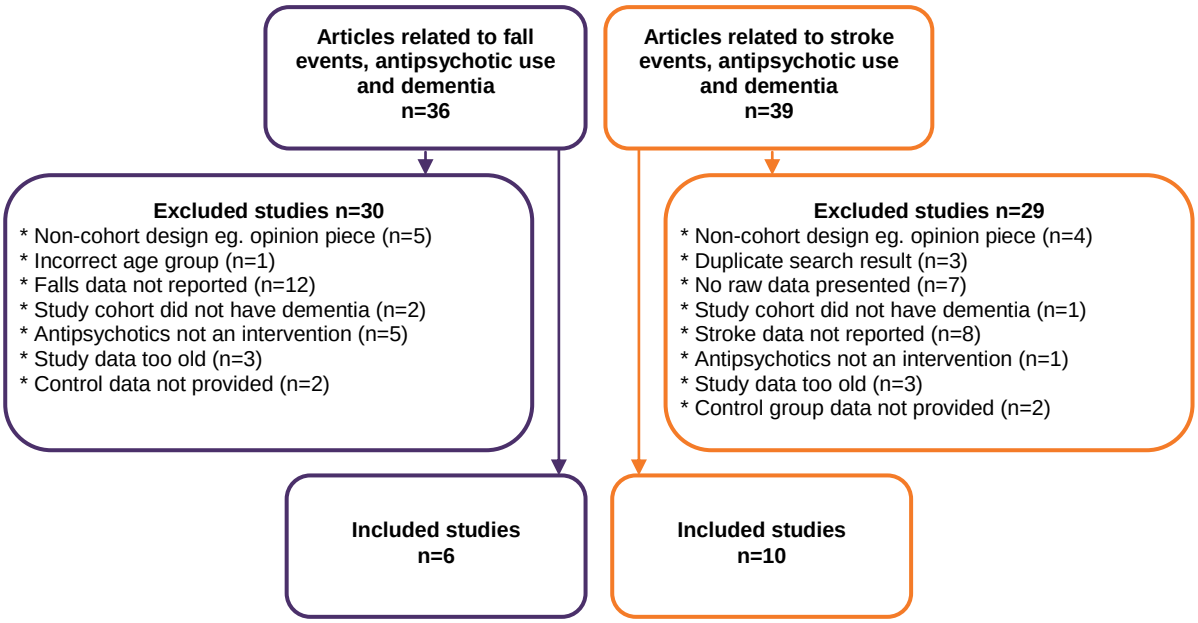
Results of Meta-Analyses

A total of 36 falls related studies were identified and 39 stroke/CVAE related studies identified. The breakdown of the sources of each study are presented in Table 1 and the reasons for exclusion have been outlined in Figure 1.

Table 1: Literature Search Terms for Studies Related to Fall and Stroke Events and Dementia With and Without Use of a Atypical Antipsychotic

Source	Search strategy	Records found
Fall events among dementia patients following use of antipsychotics		
CINAHL complete	*AB (Atypical antipsychotic* or antipsychotic*) AND AB (fall or fall risk) AND AB dementia*	10
Medline	*((atypical antipsychotic* OR antipsychotic*) AND fall* AND dementia).ab*	15
Other	*Visual inspection of reference lists from retrieved studies or studies extracted from meta-analyses*	11
Stroke events among dementia patients without use of antipsychotics		
CINAHL complete	*AB Atypical antipsychotic* AND (CVA or cardiovascular accident or stroke OR cardiovascular adverse event*) AND dementia*	7
Medline	*(Atypical antipsychotic* AND (CVA or cardiovascular accident or stroke OR cardiovascular adverse event*) AND dementia).ab*	10
Other	*Visual inspection of reference lists from retrieved studies or studies extracted from meta-analyses*	22

Figure 1: Literature Search Results



Falls data

A total of 36 studies were retrieved from the search of falls literature with 30 studies excluded (as per Figure 1). The majority of studies were excluded as they did not present fall data for the cohort with dementia. As a result, only six studies were considered for inclusion in the meta-analysis. All six of these studies examined the use of atypical antipsychotics compared to no antipsychotic use.

Cohort studies

Kolanowski et al. conducted their retrospective cohort study in 2006 using a US administrative dataset of health claims. A total of 959 individuals with dementia (defined using ICD-9 codes) aged 45 years and older had their medical history and prescription data extracted. A statistically significant difference in the incidence of falls was observed between those not on antipsychotics (7%) and those on atypical antipsychotics (14.8%) (p=0.0007). The antipsychotics under investigation were not stated. Interestingly, although not a primary outcome of the study, the study authors reported a much higher prevalence of atypical antipsychotic use among community dwellers (27%) when compared to nursing home residents (18.2%) (23).

Hien et al exclusively examined a cohort of nursing home residents who had been prescribed atypical antipsychotics for their symptoms of dementia. This prospective study recruited a total of 2,005 residents aged 65 years and older of whom 898 were non-users of antipsychotics and 120 were prescribed either olanzapine or risperidone (the remainder used typical antipsychotics). The authors of the study did not pool the results of atypical antipsychotic users when conducting significance testing of the incidence of falls when compared to non-users and as such, each antipsychotic was treated separately. The overall high rate of atypical antipsychotic use among all antipsychotic users was considered by the authors to be potentially biased as those that are more likely to fall may also be more likely to be prescribed an atypical antipsychotic due to fewer extrapyramidal side-effects that may be experienced when compared to typical antipsychotics (24). When pooled in a meta-analysis, the results of the studies demonstrated that older adults prescribed atypical antipsychotics were 2.3 times more likely to fall when compared to those not prescribed an antipsychotics (95% CI: 1.45-3.58) (Figure 2).

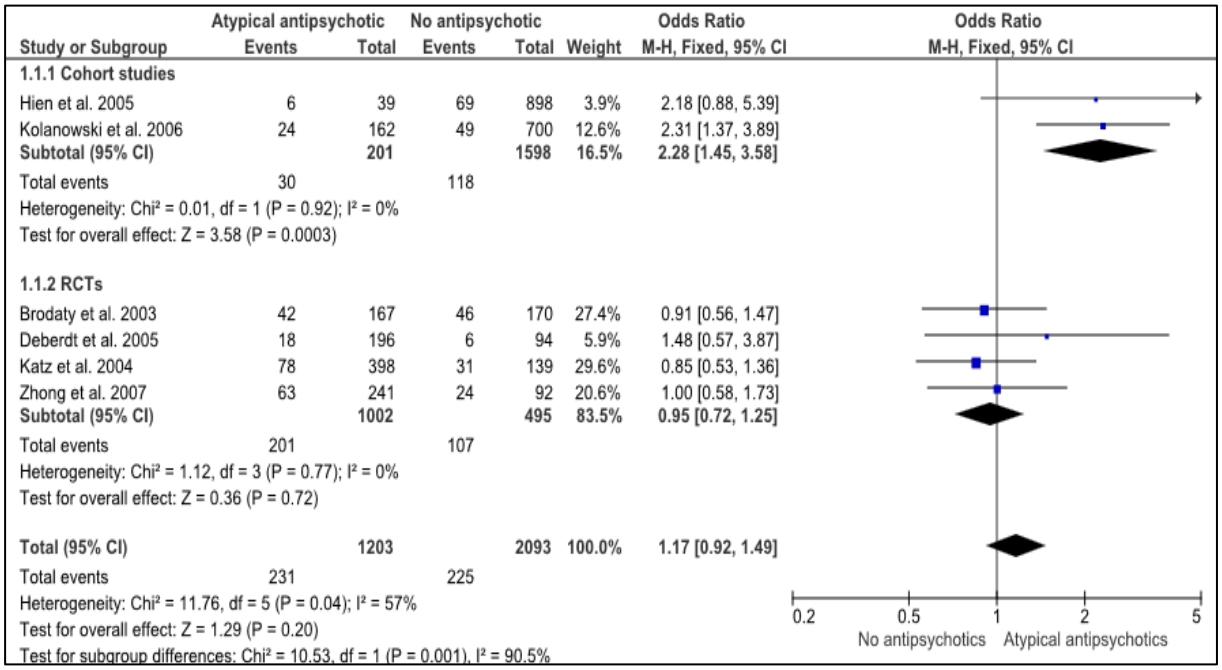
Randomised controlled trials

A total of three randomized controlled trials were pooled in a meta-analysis. The largest of the three, a paper by Katz et al, performed a secondary analysis of data from a double-blind placebo-controlled trial. The original trial from which the data pertains was investigating risperidone compared to a placebo for behavioural disturbances associated with dementia. The subset sample of 537 all had a diagnosis of dementia (DSM-IV), were ambulatory or semi-ambulatory and were all nursing home residents. No significance testing was performed to examine the risk of falling between the two study groups, however, the raw data presented shows a higher proportion of patients who fell among those not on risperidone (doses of 0.5 mg, 1 mg or 2 mg) compared with those on risperidone (22.3% vs. 19.6%). It was hypothesized by the study authors that this difference may have been attributable to this study not being powered to detect a difference in falls as the original study was powered to detect a difference in behavioural symptoms (25).

The use of risperidone was also examined by Brodaty et al among a sample of 345 nursing home residents with a diagnosis of dementia (DSM-IV), aged 55 years and older. The primary outcomes of the study were to examine aggression and behavioural symptoms between the two groups and the rate of falls (among other adverse events) were examined as a sub-analysis. Fall events were experienced by 27.1% of the placebo group and 25.1% of the intervention group with no significance testing performed on this distribution (26). A study by Deberdt et al. was included in a Cochrane Review of studies examining the use of atypical antipsychotics for aggression and psychosis in Alzheimer's disease (10). The data extracted into the systematic review was not found in the paper linked to the reference provided and despite contacting the Cochrane authors, no paper was able to be located. As per the information extracted into the review, the study by Deberdt et al was set in the USA and examined 494 patients with dementia (DSM-IV) who were prescribed either olanzapine, risperidone or a placebo over the study period of 10 weeks. Data of adverse events of a fall were only extracted for patients on either the placebo or risperidone for which there were 18 (9%) and 6 (6%) respectively.

The pooled results of the RCTs were not statistically significant nor did they illustrate an effect of atypical antipsychotics on the rate of falls among older adults with dementia (Figure 2).

Figure 2: Risk of Falls Meta-Analysis Results



The final results of the meta-analysis presented above illustrate that, when considering the data from all included eligible papers, the odds ratio of a fall event occurring is 1.17 times higher among people taking atypical antipsychotics when compared to those not on an antipsychotic (95% CI: 0.92-1.49) however, as the confidence interval indicates, this result is not statistically significant (Figure 2).

Stroke data

A total of 39 studies were retrieved from the search of stroke literature with 29 studies excluded (as per Figure 1). The majority of studies were excluded as they did not present stroke incidence data for the cohort with dementia. Ten studies were considered for inclusion in the meta-analysis with two of these studies examining the use of atypical antipsychotics compared to no antipsychotic use and three examining the use of atypical antipsychotics compared to typical antipsychotics. Each of these groups were considered separately. Due to low levels of heterogeneity within these groupings, it was not considered critical to analyse by study design and as such an RCT has been analysed alongside a cohort study.

Atypical antipsychotics compared to no antipsychotics

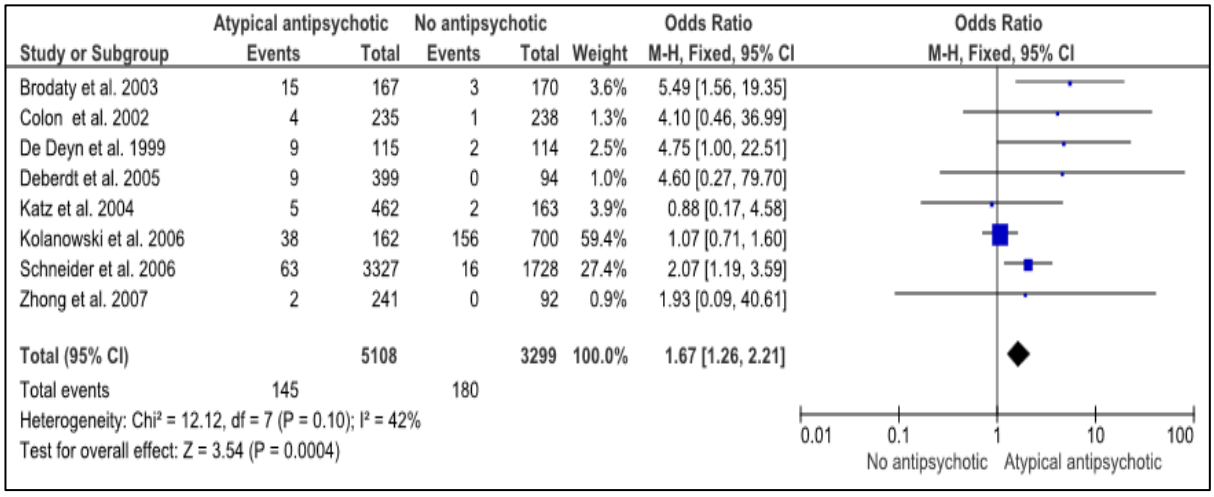
There were eight studies that compared atypical antipsychotics to no antipsychotic use of which five have been previously described (see Falls data). The largest in this group was a meta-analysis by Schneider et al that pooled data from three randomized, placebo controlled trials looking at the incidence of cardiovascular adverse events including strokes and transient ischemic events. This meta-analysis was one of the key sources that informed the development of the NPS MedicineWise antipsychotics program. The pooled sample size was over 5,000 individuals and thus has considerable weight in our meta-analysis (14).

Results of the studies by DeDeyn et al. and Colon et al. were extracted from a Cochrane review that aimed to pool studies that examined the use of atypical antipsychotics for aggression and psychosis in Alzheimer's disease (10). Colon et al. conducted a double blind, placebo, randomized controlled trial in the US involving 44 aged care facilities. The mean age of the participants was 83 years and a majority of the cohort were female. Patients were randomised to receive flexible doses of risperidone or placebo. Although both arms of the trial reported a small number of events, the overall odds ratio was 4.10 with a wide confidence interval reflective of the sample size (27). De Deyn et al. conducted a 13-week trial based in 51 European centres comparing use of Risperidone to a placebo. All participants in the trial were free from any other conditions that may have confounded the effect of risperidone on the risk of stroke such as conditions affecting cognitive function or neurological disease. There was a

statistically significant difference between the two arms under investigation with 7.8% of the atypical antipsychotic users having a cardiovascular adverse events compared to 1.8% in the placebo users (OR 4.75, 95% CI:1.00-22.51).

Data from the pooled analysis indicates that when the incidence of strokes is compared among users of atypical antipsychotics and non-users of antipsychotics, atypical antipsychotic use is associated with an 67% increased risk of stroke (95% CI: 1.26 -2.21) (Figure 3).

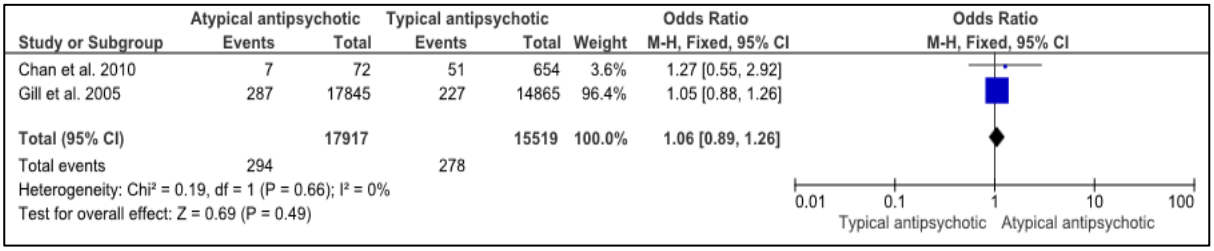
Figure 3: Risk of Strokes Meta-Analyses Results – Atypical vs No Antipsychotics



Atypical antipsychotics compared to typical antipsychotics

Both studies looking at atypical antipsychotics compared to typical antipsychotics were retrospective cohort studies. The largest of the two, a study by Gill et al., analysed data from a Canadian administrative hospital dataset linked with a pharmaceutical claims dataset. A total of 32,710 adults aged over 65 years with dementia (ICD-9) prescribed either risperidone, quetiapine or olanzapine had their data analysed. The proportion of stroke events between the two groups was very similar, 1.6% for atypical antipsychotics and 1.5% for typical antipsychotics. Gill et al. stipulate that these results may be present as, overall, all antipsychotics present a risk for stroke events and, depending on patient co-morbidities, atypical antipsychotics only slightly increase the risk overall (27). A study conducted by Hong et al utilised patient hospital records to extract data for a sample of older adults aged 65 years and over with a diagnosis of dementia and had previously made use of psychiatric services of the large hospital in Hong Kong. Atypical antipsychotics of interest included quetiapine, amisulpride, risperidone and olanzapine (doses not specified). Use of these medicines was compared to six typical antipsychotics. The overall rate of cerebrovascular adverse events (defined as a stroke or transient ischaemic attack) was only slightly higher among atypical antipsychotic users (9.7%) compared to typical antipsychotic users (7.8%). No significance testing was performed to examine whether these distributions were statistically significant (29). When pooled with the results of the trial by Gill et al. the results of the meta-analysis indicated that users of atypical antipsychotics have an increased risk of 6% of a stroke event when compared to users of typical antipsychotics, which is not statistically significant (95% CI: 0.89-1.26) (Figure 4).

Figure 4: Risk of Strokes Meta-Analyses Results – Atypical vs Typical Antipsychotics



As a statistically significant result was identified only for the studies related to CVAEs, it was decided to focus solely on this health outcome for Phase 2.

3.2 Program effectiveness

> 41% of GPs Australia wide participated in the program. Changes in GP prescribing practice, attributable to the NPS MedicineWise program, were associated with a decrease of 72,384 prescriptions, or a relative 7.3% reduction in modelled PBS prescription volume for those aged 70 years and over.

NPS MedicineWise had implemented two major programs aimed at the use of antipsychotics in general practice over the last 15 years. These were: 'Use of Antipsychotics' a non-visiting program implemented in 2007 and 'Balancing the Benefits and Harms of Antipsychotic Use' in 2011. As the 'Use of Antipsychotics' program was completed in 2007, it was not considered in this economic evaluation.

The program 'Balancing the Benefits and Harms of Antipsychotic Use (2011)' examined the management of schizophrenia, bipolar disorder and dementia with a particular focus placed on the safe and effective use of antipsychotics.

The key messages for the June 2011 program were:

- Assess benefits and harms of antipsychotic therapy
- Engage patients/carers in recognising and managing adverse effects
- Reinforce the importance of adherence to antipsychotics when prescribed
- Review ongoing need for antipsychotics for behavioural symptoms of dementia and trial withdrawal

Based on the key messages and an understanding of current prescribing practice, it was expected that the reduction in antipsychotics usage would be a more appropriate approach compared to current practice, in particular, in adults aged 65 years and over with dementia. Therefore, NPS MedicineWise expected the following trends would be observed in older people (65 years and over):

- **quetiapine:** decreased prescribing
- **olanzapine:** decreased prescribing
- **risperidone:** decreased prescribing

The reach of the NPS MedicineWise program

Participating GPs were involved in educational visits, group discussions, clinical audits and case studies. See Table 2 for the number of GP participants in each of the program interventions. Costings for the delivery of the program were based on the bulk of GP visits on this topic being delivered between August 2011 and June 2012. There were 10,737 GPs seen in total, 9,335 within that 11 month period. See Appendix 1 for more details.

Table 2: GP participation in the 'balancing the benefits and harms of antipsychotics (2011)' program

Program	Activity Type	Commencement date*	Completion date*	Unique GP participation
'Balancing the Benefits and Harms of Antipsychotics (2011)'	Clinical audit	Nov 2010	Apr 2012	576
	Case study	Aug 2011	Mar 2013	572
	Small group case based discussion (including interactive workshop)	Jul 2011	May 2013	3,748
	Educational visit	Aug 2011	Jun 2013	6,644
Total Unique GP				10,737†

* 'Activity commencement date' is the earliest participation date in any program activity. 'Activity completion date' is the date of last participation or 30 June 2014, whichever occurred first † Note, figure represents total unique GP participants and may not equal the sum of unique GPs for each individual activity

Decreased prescribing of atypical antipsychotics would be expected through two GP mediated pathways:

- Initiating non pharmacological approaches as first line therapy for BPSD (and therefore decreased initiation of atypical antipsychotics)
- Trial a withdrawal if a patient with BPSD has been on atypical antipsychotics for more than 12 weeks.

A pre and post survey of GPs (independent cross-sectional samples) and a clinical audit review was conducted to assess changes in GP knowledge, attitudes or behaviour associated with the program key messages. The PBS data is restricted to age group so the 70 years and over age group was used to analyse the costs.

In the pre-post survey, the desired response was for GPs to be in agreement with the statement; *for behavioural symptoms of dementia, non-pharmacological approaches should be recommended as first-line therapy*. In the pre survey, 81% of respondents agreed with this statement (Agree 38.8%; Strongly Agree 41.7%). There was a 7% increase (though not statistically significant) in the proportion of GPs who agreed with this statement after participating in an intervention (88%; Agree 39.4% and Strongly Agree 49%). The proportion of GP respondents agreeing with this statement was 10% higher for those who participated in an active intervention compared with those who only participated in a passive intervention (91.2% vs. 81.1%). In the audit, GPs reported that they recommended or optimised non-pharmacological approaches in 58% of their dementia patients, and at the review audit phase this had increased to 77% of their dementia patients. One of the areas where GP's indicated the greatest intention to make changes to their behaviour after participating in the audit was trialling non-pharmacological approaches as first-line therapy for BPSD (30.1% of audit participants).

3.3 Drug utilisation analysis

Age stratified PBS data was only available for data from July 2008 onwards and as a result the time series data of antipsychotics appeared to be sensitive to the relative shorter time period as well as two significant price drops occurring in December 2008 (risperidone) and April 2012 (quetiapine and olanzapine). This may have distorted the estimate of an NPS MedicineWise program effect as the price reductions would have also resulted in savings. The model based on prescription volume can cater for the price change, hence is considered primarily for a saving estimate. The change in volume was then converted to a saving in expenditure based upon an average net price per prescription, per month for the overall population. Although the target group was those aged 65 and over, the analysis

was carried out for people who are aged 70 and older due to the availability of this age grouping in the PBS data and, as such, the majority of this age group are concession card holders. Concession card holders are more expensive for the Government as they cover more of the costs. We report total savings for the period from July 2013 to June 2014.

Results

The reduction in antipsychotic prescription volume had a statistically significant association with the 'Balancing the Benefits and Harms of Antipsychotics (2011)' program. As shown in Figure 5 the yellow shaded area between the estimated volume with the NPS MedicineWise program included (red line) and the estimated volume of prescriptions without the program (green line) presents the impact of the program in reducing the volume of drugs prescribed.

As shown in Figure 5, plot of the 'estimated volume with intervention', PBS volume closely follows the 'actual PBS prescription volume'. This indicates that the time series model fits the data well.

We considered major external events that could potentially affect the trajectory of the volume series and confound evaluation of the NPS MedicineWise intervention program, however for the analysis of the time series data for people aged 70 and over, no external major events were identified.

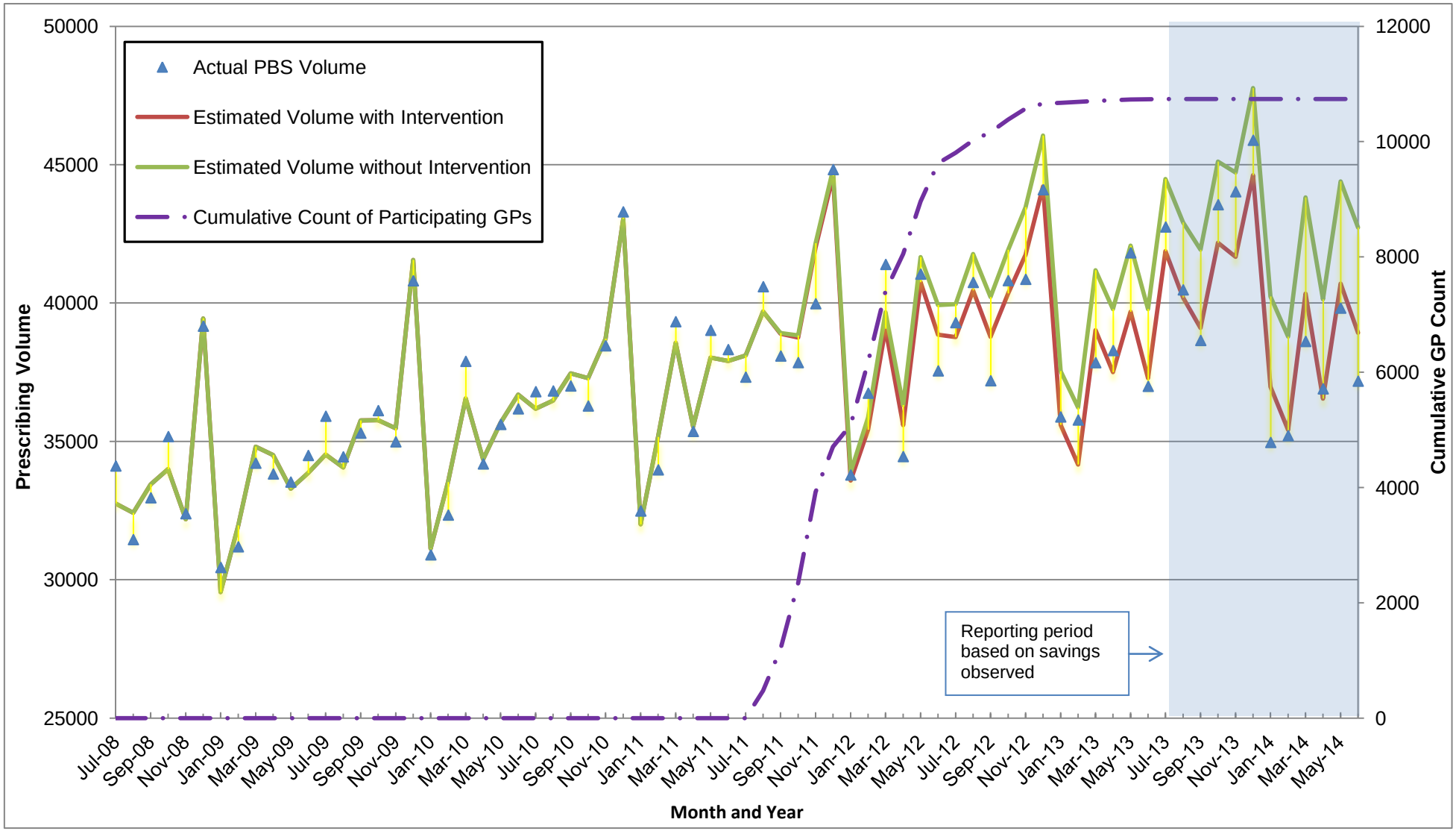
Using the model diagnostics criteria outlined in the methods section the no-decay model is the best fitting model and Figure 5 depicts the model with no-decay of the effect of the NPS program.

Savings estimate attributable to the NPS MedicineWise program

Approximately 41% (N= 10,737) of GPs Australia-wide participated in the NPS MedicineWise visiting program 'Balancing the Benefits and Harms of Antipsychotics (2011)'.

Changes in GP prescribing practice, attributable to the NPS MedicineWise program, were associated with a decrease of 72,384 prescriptions, or a relative 7.3% reduction in modelled PBS prescription volume. It is estimated that the NPS MedicineWise program reduced government expenditure on antipsychotics in adults 70 years of age and over, for the 2011-14 financial years, by $4.27 million.

Figure 5: Impact of the NPS program 'balancing the benefits and harms of antipsychotics (2011)' on PBS volume of olanzapine, quetiapine and risperidone used in the management of psychiatric disorders and BPSD for those aged 70 and over, after allowing for covariates and assuming NO decay of the NPS message



3.4 Cost Benefit Analysis

Cost Benefit Analysis Design

The analysis involved a decision tree model to allow for investigation into the following elements:

- The *effects* of the intervention on incidence of stroke and falls and related hospitalisations.
- The *benefits* of the interventions in terms of the monetary value of effects generated by the NPS intervention

The study has focussed on the perspective of the health system funder, both federal and state. Only direct costs to the health system are assessed. The programmes' consequences were valued in monetary units, enabling us to make a direct comparison between participation and non-participation in the NPS program.

In particular, decision analysis in the form of a decision tree model has been used to undertake these analyses as multiple decision options are able to be entered into a model with respective consequences. A decision tree typically contains three stages of movement denoted by decision nodes, chance nodes and terminal nodes. The options following from the decision nodes and chance nodes are given probabilities that can be taken from a number of sources such as RCTs, observational studies or previously published literature.

A decision tree model outlines decisions (that is, to provide an intervention or not), the probability or fraction of various outcomes (that is, proportion of patients having a stroke), and the valuation of each outcome (that is, the cost of a patient being hospitalised following a stroke). The mean value of a decision is computed analytically by summing the probability of each outcome with its value.

Time frame

The main intervention time period was from August 2011 to September 2013, although formative research commenced in July 2010. This time frame excludes the time taken to complete cost savings. The analytical time frame occurred between June 2011 and June 2014. This is due to the short time frame during which adverse events of antipsychotics occur. The evidence suggests that the risk of a stroke in dementia patients is highest in the first 12 weeks post initiation of an antipsychotic.

Data sources

Data from the NPS MedicineWise clinical audit, GP surveys and the PBS cost savings report were utilised, all undertaken as part of the evaluation of the antipsychotics program. In addition, literature and reports were sought regarding prescribing and management practices of GPs for dementia. Incidence and outcome probabilities were also extracted from the literature and meta-analysis.

Assigning probabilities

Each intermediate action or outcome is assigned a probability of occurrence, the sum of probabilities assigned to the possible events emanating from one chance node is equal to 1. In the model, the prevalence of GPs in each arm and their probability of receiving the intervention have been derived from the internal audit and outcome probabilities (point estimates and corresponding ranges) were derived from the meta analysis. Each outcome is also assigned a payoff (eg. total cost or effectiveness), which represents the net value corresponding to the specific path (ie. the sequence of events leading up to that outcome). With respect to effectiveness, we considered the number of hospitalisations prevented to be the measure of effectiveness by assigning 1 to the outcome "no event" and 0 to all other outcomes.

The calculation process moves from right (terminal nodes, corresponding to the outcomes) to left (initial node) with each payoff (total cost or effectiveness, alternatively) multiplied by the probability of the corresponding branch, and then added to the same value obtained for the opposite branch

(emanating from the same node), thus producing the expected value of the chance node considered (ie. the weighted average net value for each chance node). This process is iterated moving backward to the initial node, at which point the expected values calculated for the two periods can be compared (and the arm that allows for the best result can be identified eg. the lower cost or the higher effectiveness).

Outcome costs

Costs related to the public and private hospitalisation and post-hospitalisation phases following a stroke were extracted from two key AIHW reports (13, 30). As the costs were for the time period 2009/2010, the prices were inflated to 2012/2013 equivalents using the AIHW implicit price deflater which is specific to inflation rates for healthcare associated costs (31).

Data analysis

Following the construction of the decision tree, the probabilities are *averaged out* from right to left to calculate the expected values of each strategy. This involves multiplying the outcome of each branch by the respective probability. Probabilistic sensitivity analysis was performed to address any parameter uncertainty for each of the probabilities (which will be presented as ranges). Monte Carlo simulation was performed for this sensitivity analysis and has reported 95% confidence intervals for each of the outcomes of interest. Cost effectiveness acceptability curves were also produced.

Uncertainty

Using Treeage software, sensitivity analysis was conducted among dementia patients for stroke odds ratios and range of medicines used.

Results

The decision tree model suggests that 177 strokes or cardiovascular adverse events could have been avoided for the 2011-14 financial years as a result of the NPS MedicineWise program. We have taken a three year period to model the number of strokes and cardiovascular adverse events as these were modelled on the volume of antipsychotics not prescribed in dementia patients.

The cost of stroke related hospitalisation per older adult with dementia is $12,990.40 (39). This is a similar figure used by the Deloitte Access report (18). We could not find a source for the cost of a CVAE hospitalisation per older adult with dementia. We can assume we have saved a maximum of $2,229,230 to the hospital system.

It is estimated that the NPS MedicineWise program, for the 2011-14 financial years reduced government expenditure to the PBS through reduction in antipsychotics, by $4.27 million and to the state hospital system an estimated $2.23 million as a reduction in stroke/CVAE hospitalisation of older adults with dementia. This is a total saving to the health system of $6.5 million.

QALYs

Based on the study conducted by the Institute for Innovation and Improvement, the incremental QALY gain per avoided stroke is 0.20 and the incremental QALY gain per avoided fall is 0.09 (5). The QALYs gained were valued at A$50,000/QALY as commonly used in economic evaluations valuing health outcomes. It is estimated the value of the QALYs gained due to NPS MedicineWise interventions averting strokes in dementia patients is $1,770,000 given that 177 strokes were averted.

Table 3: Savings to the health system and quality life gains from reduced antipsychotic prescribing for older people with dementia

Parameter	Cost of Antipsychotic drug use	Cost of NPS Intervention	Difference in cost
Total cost of intervention	$6,500,000	$4,428,060	$2,071,940
QALY #Net QALY gain from strokes averted +Total monetary value of QALY gain			 35.4 $1,770,000
Net Benefit **Benefit to cost ratio**			$3,841,940 2.4*

* Values higher than one indicate that the benefits exceed the costs, and thus the intervention represents an efficient use of public resources.

#The net QALY gain from strokes averted is the number of stokes averted multiplied by 0.20 (incremental QALY gained from each stroke averted):

Net QALY gain = 177 stroked averted x 0.20 = 35.4

Total monetary value of QALY gain = 35.2 x $50,000 = $1,770,000

The net benefit is the difference in the cost of antipsychotic drugs without the intervention compared to the cost of the NPS intervention and the total monetary value of QALY gain:

Net benefit = $2,071,940 + $1,770,000 = $3,841,940

The benefit to cost ratio is calculated by dividing the estimated cost of antipsychotic drug treatment by the cost of the NPS intervention (after subtracting the QALY gain):

Benefit to cost ratio = 6,500,000/(4,428,060-1,770,000) = 2.4

DISCUSSION

The economic evaluation of the NPS MedicineWise program 'Balancing the Benefits and Harms of Antipsychotic Use' found that:

- the odds of experiencing stroke events and CVAE is higher in those using atypical antipsychotics, although it is not for falls;
- the NPS MedicineWise program was effective in decreasing GP prescribing of atypical antipsychotics for older people with dementia with a 7.3% reduction in modelled PBS prescription volume, saving $4.27 million in PBS expenditure for the 2011-2014 financial years as well as $2.23 million to the state hospital system due to reductions in stroke/CVAE hospitalisation of older people with dementia. This is an estimated saving of $6.5 million to the health system over 3 years.
- The NPS MedicineWise program was estimated to have prevented 177 strokes or CVAE events from 2011 to 2014
- The cost benefit ratio was 2.4 with an estimated net benefit of over $3.8 million.

The evaluation had several limitations. This evaluation did not investigate deaths associated with use of atypical antipsychotics in this patient population. Other studies had included falls, although they are not significant, and this study excluded both falls and infectious diseases. Only PBS data for the 70 years and over age group was included in the model used.

A similar study conducted in England found that, for every £1 invested in behavioural interventions for alternatives to antipsychotic drugs for people living with dementia, there was a £1.99 saving in health care costs and quality of life gains (5). The NPS MedicineWise evaluation has found a cost benefit ratio of 2.4, which means that for every $1 invested in the NPS intervention there was a $2.40 saving in health care costs and quality of life gains, which is consistent with the study findings in England.

This evaluation has shown the NPS MedicineWise program has reached and influenced the prescribing behaviour of GPs, resulting in savings to the health care system and quality of life gains for dementia patients.

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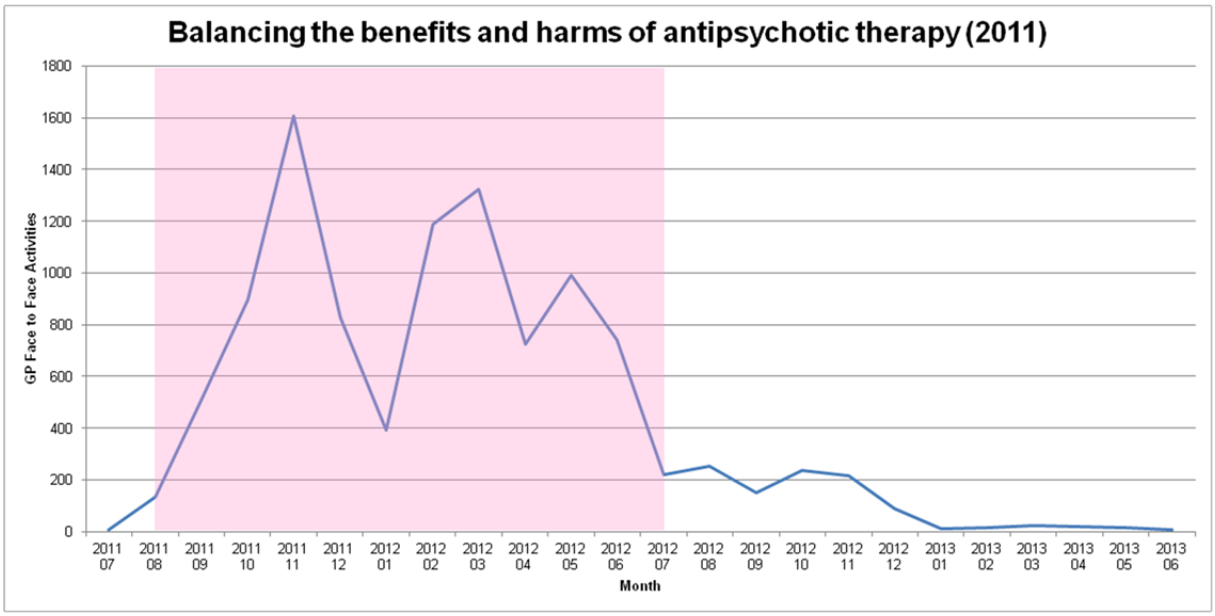
APPENDIX 1: PROGRAM COSTS

Table 4: Estimated costs associated with the development and implementation of the NPS MedicineWise Antipsychotics Program

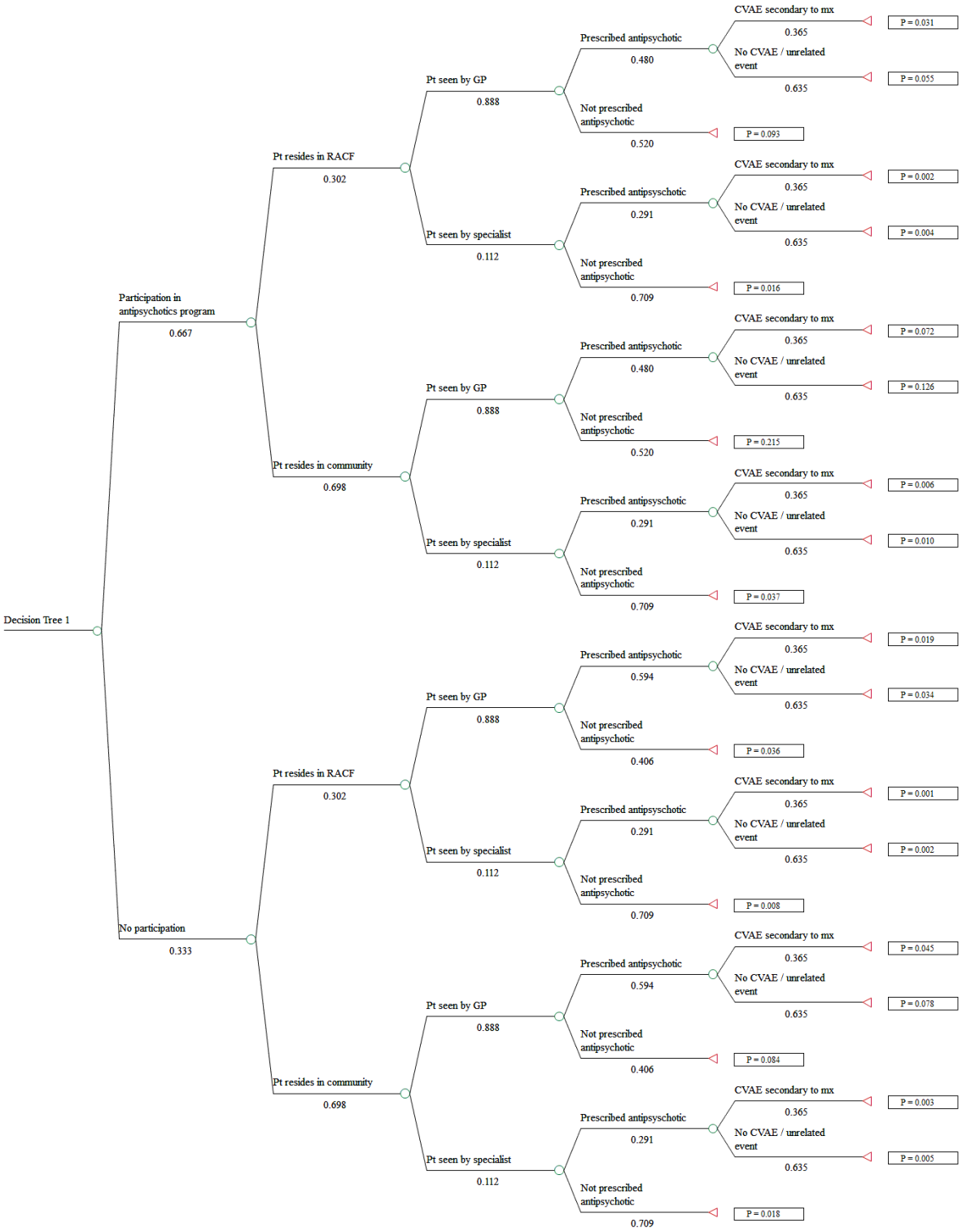
Activity	Estimated Costs
Formative research	**$40,410**
Design	**$29,461**
Development	**$499,185**
Delivery	**$3,801,261**
Evaluation	**$57,743**
Total	**$4,428,060**

Figure 6: Number of GP visits on antipsychotic topic by year and month



APPENDIX 2: DECISION TREE MODEL

Figure 7: Risk of Stroke Decision Tree1



APPENDIX 3: DECISION TREE MODEL PARAMETERS

Table 5: Parameters used to populate the decision model 1

Description (*variable name)*	**Value**	**Calculation and/or sources**
Probability of a GP in Australia actively participating in the NPS MedicineWise intervention *(p_participation)*	0.667	Number of GPs participating in the NPS MedicineWise program (2012/13) = 18,608 (32) Total number of GPs in Australia (2012/13) = 27,894 (33) Proportion of GPs in Australia reported to be actively participating in the NPS MedicineWise intervention = 18,608/27,894 = 0.667
Probability of dementia patient residing in the community *(p_community)*	0.698	(28)
Probability of a dementia patient being referred to a specialist *(p_specialist)*	0.112	(28)
Probability of a GP initiating atypical antipsychotics to a patient with dementia *(p_gp_presc)*	0.594	Number of unique GPs prescribing atypical antipsychotics during the study period (Q3 2011 - Q1 2013) = 16,278 Total number of GPs in Australia (Q3 2011 - Q1 2013) = 27,408 (34) Proportion of GPs in Australia prescribing atypical antipsychotics (Q3 2011 - Q1 2013) = 16,278/27,408 = 0.594
Probability of a GP (that has participated in the NPS program) initiating atypical antipsychotics to a patient with dementia *(p_gp_presc_nps)*	0.480	Number of unique GP's not prescribing antipsychotics = 1,075 Number of GPs passively participating in the NPS program = 7,862 Number of GPs actively participating in the NPS program = 10,746 Proportion of actively participating GPs initiating antipsychotics = (1,075 + (7,862*0.5) / (10,746 + (7,862*0.5)
Probability of a specialist initiating atypical antipsychotics to a patient with dementia *(p_spec_presc)*	0.291	Number of unique specialists prescribing atypical antipsychotics during the study period (Q3 2011 - Q1 2013) = 8,122 Total number of specialists in Australia (2011) = 25,400 (35) Average annual increase of specialists in Australia = 4.8% (35) Total number of specialists in Australia in 2013 = (1.048 * 25,400)*1.048 = 27,897 Proportion of specialists in Australia prescribing atypical antipsychotics (Q3 2011 - Q1 2013) = 8,122/27,897 = 0.291

Description (*variable name)*	Value	Calculation and/or sources
Probability of a dementia patient having a stroke (or CVAE) secondary to atypical antipsychotic use *(p_CVAE)*	0.06[1] - 0.67[2]	[1]Meta-analysis of two included studies (atypical vs. typical antipsychotics) (28, 29) [2]Meta-analysis of eight included studies (atypical vs. no antipsychotics) (14, 23, 25-27, 36-38) Mid-point probability = 0.365*

Table 6: Parameters used to populate the decision model 2

Description (*variable name)*	**Value**	**Calculation and/or sources**
Probability of a stroke related hospitalisation	0.01	Number of strokes and TIAs (defined as ICD-10-AM codes I60-I64, G45) for adults aged ≥ 65 years (2012) = 41,933 (18) Number of stroke and TIA related hospitalisations (defined as ICD-10-AM codes I60-I64, G45) for adults aged ≥ 65 years (2009/10) = 37,353 (13) Rate of stroke and TIA hospitalisation = 37,353 / 41,933 = 0.891
Cost of NPS program	$6,828,538.0 - $8,293,155.7	Mid-point cost = $7,293,416.00
Cost of stroke related hospitalisation per older adult with dementia	$12,990.4	Total cost per stroke related hospitalisation for a dementia patients (2006/2007)= $12,209 (38) Total cost per stroke (2012/2013) = $12,209 * 6.4% = $12,990.4 (31)
Cost of stroke related non-hospital care per older adult	$429.9	Number of stroke and TIA related hospitalisations (defined as ICD-10-AM codes I60-I64, G45) for adults aged ≥ 65 years (2009/10) = 37,353 (13) Total out of hospital expenditure related to stroke hospitalisations for adults aged ≥ 65 years (2009/10) = $15.1 million (13) Total cost per stroke (2009/2010) = 15,100,000 / 37,353 = $404.3 Total cost per stroke (2012/2013) = $404.3 * 6.4% = $429.9 (31)