# Antipsychotic medication dispensing and risk of death in veterans and war widows 65 years and older, 2003 and 2004: A report to the Department of Veterans' Affairs

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# EXECUTIVE SUMMARY

This report analyses the patterns of antipsychotic dispensing and associated risk of death among elderly veterans and war widows in 2003 and 2004. Antipsychotic use in the elderly has increased in the last decade and there has been growing use of atypical antipsychotic medication[1]. In general. the newer, atypical antipsychotic medications have been preferred to conventional antipsychotic medication because of the gentler side effect profile of the former[2,3].

There has been recent concern about increased mortality rates and cerebrovascular adverse events (CVAEs) in those with dementia treated with atypical antipsychotic medication [4-6]. A peer reviewed meta-analysis of randomised, controlled trials (RCTs) in dementia has shown an increased Odds Ratio of death for those receiving atypical antipsychotic medication compared with placebo (OR 1.54, 95% confidence intervals, 1.06-2.23)[7]. Other meta-analyses have demonstrated an increased risk of CVAEs with the atypical antipsychotic drugs risperidone[8] and olanzapine[5]. Although some subjects in these RCTs received the conventional antipsychotic drug haloperidol, there is limited information available on the safety of conventional antipsychotic medication from RCTs. Several database reviews have been undertaken to compare the safety of atypical and conventional antipsychotic dispensing in the elderly[9,10]. Whilst RCTs provide greater certainty about subjects and the causal effects of medication, observational database reviews are relatively inexpensive and permit scrutiny of safety at the discretion of the researcher. In addition, database reviews are able to include subjects with multiple medical comorbidities and diagnoses other than the indicated diagnosis, as well as assessing safety over a longer period.

Given the prevalence of dementia in old age[11] and the pervasiveness of behavioural and psychological symptoms in dementia (BPSD) [12], dementia is the diagnosis most likely to be associated with antipsychotic dispensing in the elderly. The symptoms for which antipsychotic drugs may be prescribed are associated with distress in individuals and carers[13]. It is therefore simplistic to consider only aspects of risk and to ignore potential benefits in quality of life that medications may deliver. The literature evaluating the benefit of antipsychotic mediation in behavioural and psychological symptoms in dementia (BPSD) is not unequivocally supportive, and warrants evaluation. The evidence for efficacy of antipsychotic medication in the treatment of aggression, agitation and psychosis in dementia rests on several trials[14-16]. However, there have been a number of trials that did not demonstrate efficacy on primary outcome measures[17-21]. The positive trials were more likely to have involved institutionalised subjects with severe dementia. Risperidone has the broadest evidence-base of support[14,16,17]. There is one study which unequivocally supports the efficacy of olanzapine in BPSD[15]. Carbamazepine and valproate are used in treatment of BPSD[22], although the evidence for their use is at best considered preliminary[22-26]. Cholinesterase inhibitors may improve some non-cognitive symptoms in dementia.

The present study, a retrospective cohort review, examined DVA entitled beneficiaries 65 years and older on 1.1.03. who were dispensed an antipsychotic drug, carbamazepine or valproate in 2003 or 2004. The cohort was divided into incident or prevalent users and analysed separately. Incident users were defined as those who were not dispensed a study drug in the 12 months before the first date of dispensing. There were two sub-analyses of incident subjects, namely, those dispensed a cholinesterase inhibitor at any time from 2001 through 2004 and those resident in an aged care facility at any time in 2003 or 2004. Gender, date of birth, date of death, postcode at 1.1.2003 and residential status were extracted from the DVA database. Details of pharmaceutical dispensing for psychotropic medication, cholinesterase inhibitors, cardiovascular dugs, drugs reflecting other cardiovascular risk

factors, drugs used in Parkinson's disease, anticholinergic drugs, drugs used to treat epilepsy, morphine, coxibs and drugs used to treat cancers were extracted. A validated measure, namely, the total number of different drugs used in the 12 months prior to first dispensing, was used as a measure of overall medical comorbidity[27]. These data (apart from anticholinergic drug dispensing) were used as covariates in the survival analysis (Cox regression) and logistic regression.

Risk of death associated with each study drug was assessed in four ways, namely, survival curves, mortality rates per 1000 person years at risk, survival analyses (Cox regression) and logistic regression in a case control analysis. Survival curves were constructed for incident and prevalent subjects in each drug group. Survival graphs were also constructed for different preparations of the antipsychotic drugs, for example, by tablet strength, oral solution or short-acting parenteral form. The second most commonly dispensed antipsychotic medication, namely, olanzapine, was chosen as the reference drug for the Cox regression. Although haloperidol was dispensed to a greater number of subjects, its broader clinical use makes comparison with other antipsychotic drugs less straightforward. Survival analyses were performed using data until 31.12.04. Subjects were followed until death, commencement of a second study drug, sixty days after discontinuation of the study drug or 31.12.04. A second Cox regression was performed with 60 day follow up in the incident cohorts. Those with cancer as a cause of death were excluded from the general incident sample and the survival analysis performed on the reduced sample. In the case control analysis, subjects were allocated a study date, namely, either the date of death or a randomly allocated date in 2003 or 2004. The pattern of dispensing for the 60 days prior to the study date was analysed and a logistic regression, adjusted for various medical covariates, performed for each cohort.

Haloperidol was the antipsychotic medication most commonly dispensed to veterans and war widows 65 years and older in 2003 and 2004 (N=5853). In the general incident cohort, haloperidol was significantly associated with increased mortality rate compared with every other study drug group (p value $<0.05$). The mortality rate for the incident haloperidol group was 909 deaths per 1000 person years at risk (95% Confidence Interval (CI) 864-957) and for the prevalent haloperidol group, 243 deaths per 1000 person years at risk (95% CI 213 to 275). The relative risk (RR) for incident haloperidol users compared with olanzapine subjects in the Cox regression over the entire time period was 2.26 (p value $<0.001$, 95% CI 2.08-2.47). The RR remained highly significant in the Cox regression with 60 days follow up (RR 2.22, p value $<0.001$ 95% CI 2.04-2.42). In the logistic regression, the Odds Ratio (OR) associated with haloperidol was significantly higher than that associated with all the other single drugs ($p<0.05$). The finding of significantly increased RR and OR associated with haloperidol dispensing was consistent across the analyses of incident and prevalent subjects. In the incident cohort there was a significant difference in survival of those dispensed haloperidol 0.5mg compared with those dispensed haloperidol 1.5mg or 5mg preparations ($p<0.001$). In the prevalent cohort there was strong evidence of a difference in survival between haloperidol 0.5mg and 1.5mg on the one hand, and haloperidol 5mg on the other ($p<0.001$).

Another study of veterans found an increased risk of death associated with haloperidol compared with olanzapine and risperidone, but this study did not adjust for medical comorbidities, age or gender[28]. In a methodologically sophisticated study, conventional antipsychotic drugs were associated with an increased RR of death compared with atypical medications[9]. Haloperidol has also been associated with an increased risk of admission for stroke when compared with atypical antipsychotic drugs[29].
There was consistent evidence in the present study that haloperidol was associated with an increased risk of death in elderly DVA entitled beneficiaries. However, haloperidol is also used in terminal agitation and the treatment of delirium[30]. Haloperidol may thus be associated with an increased risk of death because of the conditions in which it is used. In the

present study the models were adjusted for morphine and cancer drug use, the total number of different medications in the year before dispensing and drugs used in treatment of cardiovascular disease. In addition, deceased subjects were matched with the National Death Index and cancer deaths were excluded from the analysis. However, perfect matches occurred in only 53% of total deaths (4485/8417). In the Cox regression on the reduced sample, the RR for haloperidol was only reduced from 2.26 to 2.01 in the new model and remained highly significant ($p<0.001$). If the 47% of deaths that were not matched were not different from those we obtained, the RR for haloperidol would, in all likelihood, remain significant. Nevertheless, despite adjustments to the model, it may be that real, unadjusted differences remained between the haloperidol cohort and those dispensed atypical antipsychotic drugs.

The olanzapine cohort (N=4636) was the second largest antipsychotic group followed by the risperidone group (N=2444). Risperidone was associated with an increased RR of death compared with olanzapine in the general incident, prevalent and incident residential aged care analyses. The RR associated with risperidone, compared with olanzapine, in the general incident cohort was 1.23 (p value 0.003, 95% CI 1.07-1.40). The analysis in incident subjects also dispensed a cholinesterase inhibitor did not find a significant difference between RRs associated with risperidone and olanzapine, however, this analysis was much smaller (Total cohort N=2224 subjects, olanzapine N=468, risperidone N=355). In the meta-analysis by Schneider *et al.* no antipsychotic drug was associated with a significant OR by itself, the results were only statistically significant when combined[7]. In the study by Schneider *et al.* there were 1175 risperidone subjects in the analysis. The finding of increased risk with risperidone compared with olanzapine in elderly veterans and war widows may suggest a vulnerability in this population not present in subjects enrolled in RCTs. Alternatively, risperidone may have been dispensed for disorders such as delirium, which in its own right is associated with increased mortality. However, neither risperidone not olanzapine has the indication for this use and RCTs with these drugs in delirium are preliminary[31]. The results were adjusted for antidepressant drug use. Comparing drugs with similar indications for use limits confounding errors[32].

Quetiapine was associated with a significantly lower death rate than risperidone in the general incident analysis (p value $<0.05$). However, quetiapine subjects differed from other atypical antipsychotic subjects on several covariates. Whilst these particular differences have been adjusted, the quetiapine group may possess other unique characteristics for which the analyses have not been adjusted. In the prevalent cohort case control analysis, quetiapine was the only study drug not associated with a significant OR. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease (CATIE-AD) trial, due to report in 2006 using risperidone, olanzapine and quetiapine as comparators, will hopefully establish the relative efficacy and safety of these three drugs[33].

Pericyazine was the fourth most commonly dispensed antipsychotic drug in this sample. The death rate associated with incident and prevalent pericyazine subjects was not significantly different from the death rates for the atypical antipsychotic medications in these cohorts. Pericyazine subjects did not differ signifcantly from olanzapine subjects in RR of death in any analysis. Pericyazine was dispensed in its lowest strength in 93% of subjects.

Thioridazine and trifluoperazine subjects were more likely to reside in the community and less likely to have been dispensed a cholinesterase inhibitor than pericyazine, olanzapine, risperidone and quetiapine subjects. Neither of these drugs were noted to be associated with an increased RR of death compared with olanzapine subjects. Thioridazine and trifluoperazine have not been promoted as drugs to treat BPSD in recent years. In the general incident and prevalent cohorts, those dispensed carbamazepine and valproate tended to receive them entirely in the community and were less likely to have received a cholinesterase

inhibitor than the atypical antipsychotic medication groups. In these cohorts the non-dementia uses of carbamazepine and valproate may have obscured any real assessment of mortality associated with their use in BPSD. In the incident residential aged care cohort and the incident cholinesterase inhibitor cohort the death rates for carbamazepine and valproate were not significantly different from pericyazine or the atypical antipsychotic drugs. Whilst the RR for valproate was not significantly different from olanzapine, carbamazepine was associated with a significantly reduced RR of death in the residential aged care sample. Carbamazepine was associated with a significantly better survival rate than valproate in the general incident and prevalent cohorts (Log Rank test $p<0.001$). However, this may reflect different underlying diagnoses rather than a direct drug effect.

Male gender was associated with increased RR of death (RR 1.55, p value <0.001, 95% CI 1.45-1.66). Post hoc interactions between age, gender and diuretic use were constructed for each study drug. Gender was associated with a significantly increased RR in the haloperidol, olanzapine and risperidone groups. Males may have received higher doses due to concerns about aggression or agitation. Male subjects may have had more cardiovascular risk factors that were not measured in this study, such as obesity or smoking. Antipsychotic drugs may have been disproportionately dispensed to women for the treatment of mood disorders and these diagnoses may be associated with a better prognosis[34]. However, the analyses were adjusted for lithium and antidepressant drug use. Pericyazine and quetiapine were not associated with a significant gender effects,

The strengths of this review include the large number of subjects, adjustment for medical confounding variables, thorough statistical analysis, and design features measuring dispensing over time. One of the main limitations is the use of dispensing data and the assumption that the tablets dispensed were consumed. This, however, is a limitation shared by most observational retrospective cohort studies[9,10,29,35]. Pharmaceutical data rather than hospital admissions data were used to establish medical covariates. In RCTs randomisation limits the likelihood of significant confounding errors. In observational studies complex design features attempt to limit confounding errors and results must be considered in the light of these methodologies. Comparing drugs with similar indications for use limits the likelihood of confounding errors[32]. Thus haloperidol, with its broader use in terminal agitation and delirium, may be associated with increased mortality in part because of the increase in mortality associated with these conditions.

Whilst this analysis has primarily dealt with the risk of death, there is evidence from prospective trials that there is an increased incidence of CVAEs associated with antipsychotic drug use in BPSD[4,5]. Prior to death this may lead to increased disability, carer stress and hospitalisation. In the FDA analysis death was caused by cardiac events and pneumonia[6], again suggesting that increased health resources would be required prior to death. This study has not assessed the costs of using antipsychotic drugs in the elderly, however the costs may be considerably more than the price of the drugs. Therefore, given the restricted value of these drugs in BPSD, and the harm and cost associated with their use, emphasis should be placed on supporting carers and residential aged care facilities with education, environmental manipulation and evidence-based non-pharmacological interventions. On the other hand, antipsychotic drugs should be available to those with distressing symptoms who respond to these medications. However, both physician and carers need to be informed of the potential benefit and potential risk.

In conclusion, this study found that haloperidol was associated with an increased risk of death compared with other antipsychotic drugs. This is particularly important because haloperidol is dispensed to more elderly veterans and war widows than any other antipsychotic drug. There is a clear need for further studies to replicate this finding, addressing some of the

limitations in an observational retrospective cohort study such as this. Ultimately, the safety of antipsychotic drugs at various dosages can only be established beyond reasonable doubt by large RCTs. Ironically, haloperidol was considered too toxic to be included as a comparator in a large prospective, government funded trial due to report in 2006[33].

# RECOMMENDATIONS

1. It is recommended that the Department of Veterans' Affairs allows results from this analysis to be published in a peer reviewed journal. The evidence from this study needs to be assessed with findings from similar analyses by physicians and carers. Only with such information can potential risks and benefits of using these drugs in dementia be assessed.

2. It is recommended that the Department of Veterans' Affairs inform itself of the emerging literature in the area of harm associated with antipsychotic medication use in those with dementia, or even in the elderly, in order that the best information may be available to veterans, war widows, carers and treating physicians. The anticipated report of the CATIE-AD study may establish any differences in efficacy or safety among olanzapine, risperidone or quetiapine.

3. It is recommended that the Department of Veterans' Affairs should support carers and residential aged care facilities with education, environmental manipulation and evidence-based non-pharmacological interventions. These interventions may strengthen the resilience of the support system and are unlikely to cause harm.

4. Post-marketing surveillance of medications and adverse events has proved valuable in detecting longer term risks not evident in the pre-marketing, short-term efficacy trials. The Department of Veterans' Affairs, with its linkage of many databases, is uniquely situated in Australia to perform this function. This important government function may contribute to the understanding of risk associated with drug use and may inform the Department of Veterans' Affairs about the use of health resources[27].

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# 1. LITERATURE REVIEW

There has been recent concern about increased mortality rates and cerebrovascular adverse events (CVAE) in those with dementia treated with atypical antipsychotic medication[4-6]. A peer reviewed meta-analysis of randomised, controlled trials (RCTs) with atypical antipsychotic medications in dementia has shown an increased Odds Ratio of death (OR 1.54, 95% confidence intervals, 1.06-2.23)[7]. Other meta-analyses have demonstrated an increased risk of CVAEs with risperidone[8] and olanzapine[5]. Although some subjects in these randomised trials received haloperidol, there is limited information available on the safety of conventional antipsychotic medication from RCTs. The increased risk of death and CVAEs associated with atypical antipsychotic dispensing in the elderly subjects with dementia has not been replicated in RCTs with elderly subjects without dementia (written personal communication from Eli Lilly[36]). Several database reviews have been undertaken to compare the safety of atypical and conventional antipsychotic dispensing in the elderly[9,10].

In this context we have analysed the relationship between antipsychotic drug dispensing and death in DVA entitled beneficiaries 65 years and older in 2003 and 2004. This literature review will address the use of antipsychotic medication in the elderly with dementia, evidence for benefit, evidence for harm and potential mechanisms for harm. The use of other potential pharmacological treatments in behavioural and psychological symptoms in dementia (BPSD), such as, cholinesterase inhibitors, carbamazepine, valproate and antidepressant medication, will be reviewed.

The disorders for which antipsychotic drugs may be prescribed are associated with distress in individuals and carers[13]. It is therefore simplistic to consider only aspects of risk and to ignore potential benefits in quality of life that medications may deliver. The literature evaluating the benefit of antipsychotic mediation in BPSD is not unequivocally supportive, and warrants evaluation. Whilst validated rating scales exist to measure BPSD, in clinical settings the labelling of behaviours as problematic depends upon the attitudes and resources of carers and the physical care environment. Whilst a symptom may remain constant, modification of the care environment or strengthening of carers' resources may reduce the significance of the symptom. Thus caution is required when applying uni-dimensional research findings to the clinical or policy arena. Only recently have trials in BPSD examined whether an improvement in quality of life occurred with antipsychotic medication[37].

The elderly are particularly vulnerable to adverse drug reactions. Pharmacokinetic and pharmacodynamic changes in the elderly, in addition to frequent polypharmacy, contribute to this vulnerability. RCTs are often short-term and have stringent exclusion criteria. As many of the RCTs are initiated or sponsored by the pharmaceutical industry, it is pertinent to examine not only what is known, but what other questions should be asked. Whilst RCTs provide greater certainty about subjects and the causal effects of medication, database reviews are relatively inexpensive and permit scrutiny of safety at the discretion of the researcher. Database reviews include subjects with multiple medical comorbidities and diagnoses other than the indicated diagnosis, as well as assessing safety over a longer period.

## 1.1 CLASSIFICATION OF ANTIPSYCHOTIC MEDICATION

Conventional antipsychotic medications include haloperidol, pericyazine, chlorpromazine, thioridazine, trifluoperazine and fluphenazine. Conventional antipsychotic drugs can also be constituted as long-acting depot preparations which are more commonly used in schizophrenia and related psychoses. Conventional antipsychotic drugs are relatively

inexpensive, unlike the atypical medications. Atypical antipsychotic drugs include clozapine, risperidone, olanzapine, quetiapine, amisulpride and aripiprazole. Risperidone is available in a long-acting depot preparation. Atypical antipsychotic medications differ in action and side effects from conventional antipsychotic drugs. Atypical antipsychotic drugs have often been used in place of conventional antipsychotic drugs because of their perceived benign side effect profile[2,3]. Antipsychotic drugs have diverse chemical structures. For details of drug-specific side effects see Appendix 3.

## 1.2 ANTIPSYCHOTIC USE IN THE ELDERLY

In the elderly, antipsychotic medications are used to treat psychosis and behavioural problems in dementia, delirium, agitated depression, bipolar affective disorder and schizophrenia and related psychoses. Antipsychotic drugs are also used in palliative care for agitation occurring at the end of life. Haloperidol and chlorpromazine are commonly used by palliative care physicians[30]. In addition, haloperidol is often used in delirium. Risperidone and olanzapine are at times used in treatment of delirium, although this is not an approved indication for either drug.

Antipsychotic use in the elderly has increased in the last decade and there has been growing use of atypical antipsychotic medication. In an Ontario database review, elderly subjects dispensed antipsychotic drugs rose from 2.2% of the total elderly in 1993, to 3.0% of the total elderly by the end of 2002[1]. The total antipsychotic drug cost increased by 729% over this period. Atypical antipsychotic medication contributed to 95.2% of total antipsychotic drug costs in 2002.

Antipsychotic drugs are used in the treatment of behavioural and psychological symptoms in dementia (BPSD). BPSD are arguably the most common indication for which antipsychotic drugs are prescribed in the elderly based on the prevalence of dementia, the frequency of BPSD within dementia and the tendency to address these problems, at least in part, pharmacologically.

A meta-analysis of dementia prevalence studies found that the prevalence for dementia doubled every 5.1 years from the age of 60 years until the age of 95 years[11]. In this analysis, the prevalence for those aged 85-89 years was 20.8%[11]. In a longitudinal Scandinavian study, the prevalence for those 85 years and older was 30%[38]. In a longitudinal, community study of dementia subjects, 62% were found to have at least one neuropsychiatric symptom at baseline, and 81% of these subjects had at least one symptom at 18 month follow up[39]. The strength of this study was the population-based sample. Studies recruiting subjects from clinical sources have shown an even higher prevalence of neuropsychiatric symptoms[40]. Ninety percent of residents in residential aged care facilities have dementia[41]. Over 90% of residents with dementia in aged care facilities had at least one behavioural or psychological symptom and 60% displayed psychotic symptoms[12].

The widespread use of antipsychotic medication in residential aged care facilities has been well documented. In one recent UK study 41% of residents with dementia were prescribed an antipsychotic drug[41]. In an Australian study, Snowdon, 1999, reported that 22.6% of nursing home residents were prescribed an antipsychotic medication[42]. In a more recent article, describing the antipsychotic drug use in 40 Sydney nursing homes, 25.1% of residents were dispensed these drugs[43]. A well designed retrospective database review from Ontario analysed the drugs dispensed to new nursing home residents, 66 years and older[44]. Seventeen percent of residents not prescribed antipsychotic drugs on admission were commenced on one within 100 days. By the end of the first year, 24% of residents had received an antipsychotic drug. In community samples those with dementia were six times

more likely to be taking an antipsychotic drug than those without dementia (30% versus 5%)[45]. Given the prevalence of dementia in old age and the pervasiveness of BPSD, dementia is the diagnosis most likely to be linked with antipsychotic drug dispensing.

The high prevalence of both psychotic symptoms and antipsychotic drug use in dementia suggest that medication may not always be effective. Indeed, some authors argue that delusions in dementia that are understandable on the basis of memory impairment may be phenomenologically different from delusions occurring in schizophrenia[46]. Hence, assumptions about treatment response in schizophrenia should not be applied uncritically to the treatment of psychotic symptoms in dementia. Other pharmacological options for the treatment of BPSD, namely, cholinesterase inhibitors, sodium valproate, carbamazepine and antidepressants, will be discussed later.

Antipsychotic medication is dispensed for disorders other than BPSD. However, in those over 65 years the prevalence of dementia outstrips the prevalence of schizophrenia, schizoaffective disorder and psychotic depression. The 6 month community prevalence for schizophrenia or schizophreniform disorder in those 65 years and older ranged between 0.0% and 0.9% in three centres[34]. The prevalence of major depression without bereavement ranged between 1.0-1.6% in those over 65 years. Not all of these depressed subjects would have been dispensed an antipsychotic medication to treat the mood disorder. In the same study, there were no subjects with a manic episode. The prevalence of mild cognitive impairment in those over 65 years, as assessed solely by the Mini-Mental State Examination, ranged from 11.6-16.6%. The prevalence of severe cognitive impairment ranged from 3.6-4.2% in those 65 years and older[34].

## 1.3 EFFICACY TRIALS OF ANTIPSYCHOTIC MEDICATION USE IN DEMENTIA

Schneider *et al.* produced a meta-analysis of antipsychotic drug trials in dementia from 1954 to 1989[47]. Whilst none of the studies met Schneider and colleagues' standards for statistical significance, methodologically acceptable studies, when combined, produced an effect size of 0.18 with a two-tailed p value of 0.008. Thus there was strong evidence for a small effect size in randomised control trials for antipsychotic medications in dementia. Some of the earlier studies did not use validated rating scales and only one of the studies was adequately powered to detect an effect size of 0.18. There was no evidence of superiority of thioridazine or haloperidol when compared with an active comparator.

Table 1 (beginning on the following page) presents a summary of recent trials of antipsychotic medication for elderly patients with dementia. In the table, a distinction is made between trials using subjects with Alzheimer's disease (AD) and those using subjects with mixed dementia diagnoses.

*Table 1. Antipsychotic medication trials*

| Author and year | Population & symptoms | Study design, length and treatment | Main outcome measure | Result |
|---|---|---|---|---|
| Golberg and Goldberg 1997[48] | Behavioural disturbance in dementia, NH | Risperidone group (N=109), Not well described ?flexible dosage Risperidone 0.25mg twice daily (N=53), 0.5mg twice daily (N=54), more than 0.5mg twice daily (N=2), 62 AP naive | Nursing staff questionnaire (not a validated instrument) | 46 patients discontinued. No blinding, no placebo group. Rated as "helpful" by staff in 38/100 patients, "moderately helpful" in 26/100. |
| Devanand *et al.* 1998[49] | Psychosis or disruptive behaviour in AD, Community (memory clinic) | Randomised, double-blind placebo-controlled cross-over design, 6 weeks per arm, Haloperidol 2-3mg (N=13/20 first arm, N=8 second arm), Haloperidol 0.5-0.75mg(N=17/20 first arm, N=10 second arm), placebo (n=20) 71 subjects randomised, 60 completed first crossover arm, 49 completed second arm, Mean MMSE 19.4 | Brief Psychiatric rating Scale (BPRS), Schedule for Affective Disorders and Schizophrenia (SADS) psychosis and disorganisation sub-scores, Behavioural Syndromes Scale for Dementia, subscales for agitation and aggression | No significant difference between low dose haloperidol and placebo in efficacy or SE. Significant difference favouring high dose haloperidol compared with low dose haloperidol on BPRS sub-scales in first cross-over arm. No significant difference between doses on second arm. High haloperidol dose significant increase in EPSE. |
| De Deyn *et al.* 1999[17] | Dementia (AD and VaD), NH or institution | RCT, flexible dose, intention-to-treat, 13 weeks, Risperidone (N=115) mean dose 1.1mg/day, Haloperidol (N=115) mean dose 1.2 mg/day, Placebo (N=114), mean MMSE 8-9, Mean age 81 | At least 30% reduction in Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD), Cohen-Mansfield Agitation Inventory (CMAI), Clinical Global Impression Scale (CGI), | At least 30% reduction in BEHAVE-AD at endpoint: risperidone 54%, haloperidol 63% and placebo 47%. No significant improvement with risperidone in BEHAVE-AD at end point. Aggression scores showed significant improvement with risperidone compared with placebo. CMAI significant decrease with risperidone compared with placebo. Over a third discontinued. |
| Katz *et al.* 1999[14] | Psychotic and behavioural symptoms in dementia, NH | RCT, fixed dose risperidone 0.5mg (N=149), 1.0mg (N=148), risperidone 2mg (N=165), Placebo (N=163), 12 weeks, Mean MMSE 6.6, Mean Age 82.7, Previous AP treatment 82% | Greater or equal than 50% reduction in BEHAVE-AD total score. Secondary measures CMAI, CGI scale | Risperidone 1mg and 2mg sig improvement in BEHAVE-AD total score. Risperidone 1mg and 2mg sig improvement in BEHAVE-AD psychosis and aggression subscale. Risperidone 2mg significant increase in EPSE and 42% discontinuation |

| | | | | |
|---|---|---|---|---|
| Cohen-Mansfield *et al.* 1999[50] | Dementia, NH N=35 completed, N=23 discontinued | Double-blind cross-over trial, 17 weeks, Withdrawal of lorazepam, haloperidol or thioridazine, | BPRS, CMAI | No significant change during placebo arm. Patients discontinued from study by nursing staff, half were on placebo and half were on usual medication. 23/58 discontinued. |
| Teri *et al.* 2000[21] | Agitation in dementia (AD), Community, | RCT, double blind, 16 weeks, Haloperidol (N=34), Trazodone (N=37), Behavioural management (N=41), Placebo (N=36) | Clinical Global Impression-Severity (CGI-S) | No significant difference in efficacy across groups. Reason for discontinuation differed significantly. |
| Street *et al.* 2000[15] | Psychotic features or behavioural disturbance in AD, NH | Fixed dose double blind, RCT, 6 weeks, Placebo (N=47), Olanzapine 5mg (N=56), Olanzapine 10mg (n=50), Olanzapine 15mg (N=53), Mean MMSE 6.9, Mean age 83 | Agitation/aggression, delusions and hallucination sub-scale of Neuropsychiatric Inventory-Nursing home version (NPI/NH), | Olanzapine 5mg and 10mg dose sig better than placebo on NPI/NH subunits. Olanzapine 15mg no sig. improvement compared to placebo. Somnolence and gait disturbance, Significantly more discontinued in Olanzapine 15mg group |
| Street *et al.* 2001[51] | BPSD in dementia, NH | Open-label extension, flexible dose, 18 weeks, Olanzapine mean dose 7mg/day, (N=105), 70 completed | NPI/NH subset total, BPRS, CGI Severity of Alzheimer's scores | Some NPI/NH subunits significant improvement (irritability, agitation, delusion), Significant improvement on NPI/NH subset total, BPRS total, |
| Chan *et al.* 2001[52] | BPSD in Chinese patients with dementia, inpatients and outpatients | Double blind, randomised head to head, trial of risperidone 0.5mg to 2mg/day (N=29), mean dose 0.85mg/day, haloperidol 0.5mg to 2mg/day, mean dose 0.9mg/day (N=29), 12 weeks, Mean age 80.5 | CMAI, BEHAVE-AD, Simpson-Angus Scale and Mini-Mental State Examination (MMSE) | Both treatment groups significantly reduced scores on CMAI. Risperidone sig reduction on BEHAVE-ED multiple subscales, whilst haloperidol only on aggression sub-scale. No sig differences between groups on efficacy. Haloperidol significant increase in EPSE. |
| Pollock *et al.* 2002[53] | Psychosis and behavioural disturbance in non-depressed hospital patients with dementia | RCT, up to 17 days, Citalopram (N=31), perphenazine (N=33), placebo (N=21) | Neurobehavioural Rating Scale | 54% discontinued, Citalopram but not perphenazine was significantly different from placebo on total scale. Both active treatments had significant improvement on subscales agitation, psychosis and lability |

| | | | | |
|---|---|---|---|---|
| Brodaty *et al.* 2003[16] | Aggression, agitation and psychosis in dementia, NH | RCT, 12 weeks, flexible dose risperidone max 2mg, mean risperidone dose 0.95mg/day, Placebo (N=170), Risperidone (N=167), Mean MMSE risperidone group 5.14, Mean age 83 | CMAI aggression subscale, (secondary, CMAI other subscales, BEHAVE-AD, CGI-S and Clinical Global Impression of Change (CGI-C) | Significant reduction in aggression and non-aggression CMAI subscales, BEHAVE-AD total and psychotic subscale and CGI-S and CGI-I for those on risperidone, Non-sig difference in EPSE risperidone vs. placebo. Pneumonia (3 vs. 1)and stroke deaths (2 vs. 0). 6 CVAE in risperidone group. 27% risperidone discontinued, 33% placebo discontinued, |
| Fontaine *et al.* 2003[54] | Behavioural disturbances in dementia, NH | Double blind, randomised, head to head trial, Olanzapine 2.5mg–10mg, mean 6.65mg/day, (N=20), Risperidone 0.5mg-2mg, mean 1,47 mg/day(N=19), 2 weeks | CGI and NPI/NH | Significant reduction from baseline for both active comparators. No sig difference between drugs. |
| De Deyn *et al.* 2004[55] | Behavioural and psychotic symptoms in AD, NH or continuing care | RCT, 10 weeks, fixed dose, Olanzapine 1mg (N=129), 2.5mg (N=134), 5.0mg (N=125), 7.5mg (N=132), placebo (129), Mean MMSE 13.7, 48% of sample agitated on the NPI/NH agitation scale | NPI/NH psychosis total scores, second primary measure CGI-C, | Endpoint pair wise comparison did not show significant difference compared with placebo. LOCF analysis NPI/NH showed sig improvement for Olanzapine 7.5mg group compared with placebo. NPI/NH subscale of aggression/agitation showed significant improvement for 1mg, 2.5mg and 7.5mg compared with placebo. Pneumonia deaths: 5 in olanzapine groups |
| Suh *et al.* 2004[56] | BPSD, dementia, NH, Korean | Double blind cross-over trial (N=120), flexible dose Risperidone, mean dose 0.80mg, haloperidol mean dose 0.83mg, 18 weeks, Mean MMSE 9.6, Mean age 80.9 | BEHAVE-AD total, CMAI Korean version (CMAI-K), CGI-C | Risperidone superior to haloperidol on BEHAVE-AD total, CMAI-K total and CMAI-K subunits |
| Ballard *et al.* 2004[57] | AD on AP for at least 3 months and no severe behavioural disturbance, NH | 3 months double blind placebo controlled discontinuation of AP, Active (N=54), placebo (N=46) | NPI, Dementia Care Mapping | High NPI score, active less disruptive than placebo group, Low NPI score <=14, no difference between active or placebo group. Trend toward improved QoL in those withdrawn from active drug but not significant. |

| | | | | |
|---|---|---|---|---|
| Deberdt *et al.*2005[19] | Psychotic symptoms in dementia, residential and community subjects | Olanzapine (N=204), risperidone (N=196), placebo (N=94) 10 week RCT, Mean MSE 14.4 | 30% reduction NPI or NPI/NH-psychosis subscale, CGI-Severity of Psychosis scale | Efficacy did not differ between groups. Both active groups significantly more somnolence, urinary incontinence and hostility. Risperidone more gait disturbance. Discontinuation in olanzapine group greater than placebo |
| Ballard *et al.*2005[37] | Agitation in dementia | RCT, 26 weeks, N=31 randomised to each group but rivastigmine (N=22), quetiapine (N=23), placebo (N=26) started, Investigator initiated, no direct drug company sponsorship, Mean age 83.8 | CMAI, Severe impairment battery | No significant reduction in agitation in either active group compared with placebo at 6 or 26 weeks. Quetiapine group significantly worse on cognitive testing at 6 and 26 weeks |
| DeDeyn *et al.*2005[18] | Psychosis in AD, Outpatients | Aripiprazole (N=106), Placebo (N=102), Mean aripiprazole dose at endpoint 10.0mg/day, 10 weeks, mean MMSE 14.2 | NPI psychosis subscale, (secondary BPRS, CGI-S) | NPI psychosis subscale, all groups improved, no improvements were sig compared with placebo. Total BPRS not sig at endpoint. some BPRS subunits significantly different. |
| Mintzer *et al.* 2006[20] | Psychosis in AD, nursing home residents | RCT, 8 weeks, Placebo (N=238), Risperidone 1.0mg to 1.5mg/day (N=235), mean dose 1.03mg/day. Mean MMSE 13.2, Mean age 83.4 years | BEHAVE-AD Psychosis subscale and CGI-C | No sig difference on outcome measures. Sub-analysis: MMSE<10 sig change on CGI-C with risperidone. Deaths, risperidone vs. placebo, 3.8% vs. 2.5% |

Not all trials in Table 1 are sufficiently well designed and powered to be able to provide meaningful results. Some trials had small numbers, investigators were not blinded or there was no placebo control[48,50,52-54]. These shortcomings reflect the difficulty of performing trials in this area without significant, usually pharmaceutical company, funding. Some trials were so brief as to be meaningless, given an understanding of the time taken to reach steady state and achieve neuroreceptor modulation[53]. Many of the larger RCT were 6 to 16 weeks. Whilst this may be adequate to assess efficacy, it does not provide information about adverse events occurring in the longer term. The exceptions were trials by Tariot *et al*., 2000, Street *et al.,* 2001 and Ballard *et al.,* 2005, which lasted 52, 18 and 26 weeks respectively[37,51,58]. The trial by Tariot *et al.* was an open-label trial in elderly subjects with a range of diagnoses[58].

There was evidence of large placebo responses in some trials [19,21,55]. Studies without placebo groups comparing two active treatments should be viewed with caution [52,54,56], because claims that both drugs are equally effective are meaningless unless there is evidence that the drugs are more effective than placebo. Authors have postulated that subjects in trials with high placebo responses may have been less impaired and hence may have benefited from non-specific attention [19]. Two trials with large placebo responses had community-dwelling subjects with a carer, and the placebo response may be indirect evidence that support for carers can reduce the assessment of behaviours as problematic [19,21]. However, against this trend, Devanand *et al.,* 1998, demonstrated efficacy for haloperidol 2-3mg/day

over placebo, in community subjects with a mean MMSE score of 19.4[49]. In the main, studies demonstrating efficacy were conducted with severely impaired subjects (Katz *et al.* 1999 MMSE 6.6, Street *et al.* 2000 MMSE 6.9, Brodaty *et al.* 2003 MMSE 5.1) and subjects who resided in aged care facilities. It is possible that these results are not generalisable to community dwelling patients with mild impairment. It is possible that the nuances of the literature are not well known to the prescribing physicians.

Another possible explanation for the high placebo response rate was the transitory nature of BPSD, at least in some subjects. The trial by Teri *et al* [21] only required symptoms to be present for two weeks. There may be important clinical implications from the evidence of the large placebo response in trials, particularly those in which symptoms were only required to be present for a brief period. Delaying the introduction of pharmacotherapy may allow symptoms to spontaneously resolve. A critique of studies assessing the efficacy of non-pharmacological interventions is beyond the scope of this report. These interventions, however, are unlikely to be associated with harm and may support the carer whilst it is seen if the behaviour will resolve. In more recent trials, behavioural symptoms have been required to be present for longer periods of time[18].

Complex factors contributed to the high discontinuation rate in many studies. In some studies the reasons for discontinuation differed between the active drug groups and placebo groups (side effects in the former and lack of efficacy in the latter) [21]. In studies with older subjects with severe dementia, the rate of adverse events even in the placebo group was often high. Many trials analysed data from the last observation carried forward. Intention to treat analyses were rarely done. The study by Street *et al.,* 2000, was a notable exception[15].

There is a strong presumption of efficacy among health professionals, making discontinuation studies difficult to implement. The protocol in the double-blind trial of psychotropic medication discontinuation study by Cohen-Mansfield *et al.,* 1999, allowed subjects to be withdrawn from the study if nursing staff were concerned about a deterioration in behaviour[50]. There was a high discontinuation rate (40%). In half of these cases, the subject was on the original drug and not placebo. Of the 35 subjects who completed the trial, 13 remained free of psychotropic medications. The average time to reinstatement of psychotropic medication for the remaining 22 subjects was 21 days. A more recent discontinuation trial in nursing home patients with Alzheimer's disease and no severe behavioural disturbance, demonstrated that subjects with an Neuropsychiatric Inventory (NPI) [59] score <15 who discontinued antipsychotic medication were less likely to be agitated than those who remained on the antipsychotic medication[57]. In this group, there was no significant difference in other behaviours between those on placebo and active drug. The situation was different for those with a NPI score >14. In this group, those on placebo were significantly more likely to develop a marked behavioural disturbance. This study also included a measure of well-being (Dementia Care Mapping). There have been few studies that addressed the issue as to whether antipsychotic treatment improves quality of life for the recipient.

The main evidence for risperidone's efficacy was from the trials by Katz *et al.,* 1999, and Brodaty *et al.,* 2003[14,16]. The third large trial[17] did not show a significant improvement on the primary outcome measure at endpoint, however, there was a significant improvement on planned secondary outcome measures, for example aggression as measured by the Cohen-Mansfield Agitation Inventory (CMAI)[60]. A post-hoc analysis showed significant improvement on the Behavioural Pathology of Alzheimer's Disease (BEHAVE-AD)[61] aggression subscale at endpoint and 12 weeks for those receiving risperidone compared with placebo. A recent Cochrane review of the effectiveness of atypical antipsychotic medication in dementia concluded that psychotic symptoms and aggression significantly improved in

subjects receiving risperidone[62]. Two trials were sponsored by a pharmaceutical company[14,17] and one was investigator initiated with drug company funding[16]. Meta-analyses of these trials with other pharmaceutical trials first raised the possibility of increased cerebrovascular adverse events. Risperidone has received the indication for use in behavioural disturbance in dementia and was subsidised on the Pharmaceutical Benefits Scheme for this indication from 2005.

A recent large trial has failed to demonstrate efficacy for risperidone in treatment of psychosis in AD[20]. The study by Katz *et al.* 1999, however, demonstrated a significant difference in the number of subjects achieving a greater than 50% reduction in the BEHAVE-AD with risperidone [14]. In the study by Katz *et al.* the mean Min-Mental State Examination (MMSE) score was 6.6 [14], while in the recent trial the mean MMSE score was 13.2 [20]. A post-hoc analysis of subjects from the trial by Brodaty *et al.* with BEHAVE-AD psychosis subscale scores greater or equal to 2, reported significant improvement with risperidone [63]. As noted by the authors, a score of "3" on the BEHAVE-AD psychosis subscale indicated that the subject's psychotic symptoms were associated with aggression or agitation. Thus improvement of agitation or aggression may contribute to the reduction in BEHAVE-AD psychosis subscale score.

Evidence for olanzapine's efficacy in treating BPSD in nursing home residents with AD comes from a methodologically pristine trial by Street *et al.,* 2000[15]. However, other olanzapine trials have not been unequivocally positive. An unpublished Eli Lilly trial in 238 AD subjects with psychotic and behavioural symptoms did not show any significant improvement with olanzapine compared with placebo (cited in Madhusoodanan *et al., 2001* [64]). However, only 69 subjects received olanzapine 5mg or more. In another pharmaceutical company sponsored trial attempting to ascertain the most effective dose of olanzapine, treated groups were no more effective than placebo on the primary outcome measure at endpoint[55]. Another Eli Lilly study by Deberdt *et al.* compared risperidone, olanzapine and placebo[19]. There was no significant difference among the groups on any efficacy measure at any time point. It was hypothesised that this was in part due to a large placebo response. Significantly more of the olanzapine group discontinued compared with the risperidone and placebo group. Adverse events occurring significantly more often in the treated groups included hostility and urinary incontinence. Both of these symptoms are associated with increased rates of institutionalisation. The open label extension trial of olanzapine revealed mixed results[51]. The NPI nursing home version (NPI/NH) psychosis total score was not significantly reduced nor were the BPRS negative and positive clusters. There were significant reductions in agitation/aggression, irritability/lability and total score on NPI/NH. Thus the evidence of efficacy for risperidone has a broader study base than that for olanzapine.

There are apparently at least two unpublished aripiprazole trials in dementia (cited in [65]). One published trial of aripiprazole in psychosis in AD did not find significant improvement compared with placebo[18]. Most of the information about quetiapine in the elderly comes from an open-label 52 week trial. A recent RCT was by Ballard *et al.,* 2005, found that quetiapine was no more successful in treating BPSD than placebo[66]. In addition, they demonstrated that quetiapine was associated with a faster rate of cognitive decline[67]. The authors postulated that quetiapine may reduce brain derived neurotrophic factor (BNDF) or that the drug's anticholinergic activity may have interfered with cognition.

Most of the larger trials have been designed and supported by pharmaceutical companies. Exceptions include the trial by Teri *et al.* (government funded), Brodaty *et al.* (investigator initiated but funded by Janssen-Cilag), Suh *et al.* (investigator initiated but drug company funded). Ballard *et al.* (investigator funded) and the yet to report CATIE trial

(NIMH)[16,21,33,66]. Publication bias is arguably more pronounced with drug company initiated studies because it is not in the drug companies' interest to publish negative results. Schneider performed a meta-analysis of risk of death in 15 atypical antipsychotic RCTs, 9 of which were unpublished[7]. He commented that the unpublished trials did not contain an excess of adverse events but many did not obtain significant findings on the primary outcome measure.

A large government funded trial, National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), is due to report in 2006[33]. Unfortunately, this large trial does not include a conventional medication as a comparator. The investigators considered haloperidol, the most commonly used antipsychotic in the elderly Australian veterans and war widows, to be too toxic. The comparators in the CATIE trial are olanzapine, risperidone, quetiapine and a selective serotinergic uptake inhibitor, citalopram. The study design is all-embracing and will assess quality of life, health costs, safety and effectiveness.

Not all trials distinguished between subjects regarding prior exposure to antipsychotic medication. In some studies the percentage of those previously exposed to antipsychotics was over 80%[14,17]. The incomplete reporting of this feature makes meta-analysis of this variable with respect to adverse outcomes impossible. Subjects who have previously used antipsychotic medication may represent a survivor group. Naïve subjects may be more at risk. It would be pertinent to report this variable in future trials.

Whilst some studies analysed the number of responders in active and placebo groups (for example, >30% reduction in the BEHAVE-AD)[17], others analysed the overall reduction in symptom scores[15,16]. McKeith argued that the analysis should be of responders and not an overall reduction of the mean score on a measure[68]. The clinically relevant question may be the degree of improvement obtained by responders. McKeith argued that continuing prescription of antipsychotic medication should be dependent on a good clinical response[68]. Whilst it is true that medications that do not help should be ceased, the corollary is not always true, that medications associated with improvement should continue. The large placebo response and the fluctuating condition of those with dementia make it uncertain that drug dispensing causally improved behaviour. Perhaps a trial of discontinuation of medication for those whose symptoms have settled is the more nuanced application of the literature[57].

# 1.4 ASSESSMENT OF SAFETY OF ANTIPSYCHOTIC MEDICATION IN THOSE WITH DEMENTIA

## 1.4.1 Meta-analyses from peer reviewed journals, regulatory authorities and pharmaceutical companies

Table 2 (beginning on the following page) contains meta-analyses and warnings from several sources: peer reviewed journals, regulatory authorities and pharmaceutical companies.

The RCT by Brodaty *et al.,* 2003, alerted the pharmaceutical manufacturer to the increased incidence of CVAEs in those treated with risperidone. The results of a meta-analysis, which were subsequently published, showed a significant increase in CVAEs associated with risperidone treatment[4]. A subsequent meta-analysis of olanzapine by Eli Lilly, indicated a three fold increase in CVAEs and a two-fold increase in mortality[5]. There was no evidence of difference between olanzapine and risperidone in the rate of CVAEs or death in the Eli Lilly analysis. Risk factors for increased incidence of CVAEs in the olanzapine meta-analysis included age greater or equal to 80 years, vascular/mixed dementia and MMSE<14. Risk factors for death in olanzapine subjects included age >80 years, lower MMSE, sedation, dehydration, dysphagia, concomitant BZDP use and treatment-emergent pulmonary conditions.

*Table 2. Meta-analyses and regulatory warnings*

| | | | | |
|---|---|---|---|---|
| October 2002 | Health Canada and Janssen-Ortho, Wooltorton 2002 [4] Greenspan 2004 [69] | Meta-analysis of 4 RCT for risperidone N=1230 | Increased CVAE 4% risperidone vs. 2% placebo. | Suggestions: low dose, twice daily administration. Criticisms: Subjects not matched for vascular risk factors. Not all trials published |
| April 2003 | US Food and Drug Administration [70] | Meta-analysis of 4 RTCT for risperidone N=1230 | As above | As above |
| July 2003 | Jannssen-Cilag Letter to doctors [71] | Meta-analysis of 4 RCT, N=1009 risperidone subjects N=712 Placebo Three published [14,16,17], one unpubished | CVAE 3.3% risperidone vs. 1.2% placebo No increased CVAEs in non-demented elderly patients. No significant difference in mortality | Statements added to Product Information Advised to start with low dose and titrate to 1mg/day |
| 2004 | Cavazzoni *et al.* 2004 [5] | Meta-analysis of olanzapine trials, olanzapine N=1610, risperidone N=196, Conventional AP N=143, placebo N=478 | CVAEs olanzapine vs. placebo 1.3% vs. 0.4% CVAEs no sig difference risperidone and olanzapine. Mortality olanzapine vs. placebo 3.5% vs. 1.5%. No sig difference between risperidone and olanzapine | |
| March 2004 | UK Committee on Safety of Medicines [8] | Met-analysis of 4 RCT for risperidone N=1779 | Increased three fold risk CVAE risperidone. Number needed to harm re CVAEs, if treatment is over 1 year and risk constant over the year is 6.3 | Risperidone or olanzapine should not be used for BPSD. Risk likely to outweigh benefit in BPSD where there is a high baseline risk of stroke. No sig difference for mortality between risperidone and placebo. |
| March and May, 2004 | Eli Lilly, Letter to doctors [36,72] | Meta-analysis of 5 RCT, N=1662 | Increased incidence of CVAEs and mortality | Comments by Eli Lilly: Efficacy of olanzapine has not been established in psychosis in dementia and does not have the indication for use in dementia. Risk factors: >80 years, BZDP, sedation or respiratory conditions |

| | | | | |
|---|---|---|---|---|
| May 2004 | Eli Lilly, Personal communication | Integrated Olanzapine dementia clinical database N=1852 | 41.6 CVAEs per 1000 patient years. In active comparator trials incidence of CVAEs similar between olanzapine, risperidone and haloperidol | |
| March 2004 | Royal College of Psychiatrists UK, Faculty of Old Age Psychiatrists [73] | Guidelines for the management of BPSD in those with a history of stroke or TIA. | Three fold Increased risk of CVAEs | Discontinuation of olanzapine and risperidone unless there was a history of schizophrenia, moderate BPSD despite medication or serious risk of harm.<br>A range of alternative medications offered, noted poor evidence base. Consider non-pharmacological treatment, eg aromatherapy |
| 2004 | Royal College of Psychiatrists UK, Faculty of Old Age Psychiatrists [22] | Guidelines for the management of BPSD, an update | Increased risk of CVAEs | Olanzapine and risperidone had the best evidence for treatment of aggression, agitation and psychosis in dementia. Conventional AP drugs have a weaker evidence base. Quetiapine is likely to be associated with increased CVAEs as well. No single non-pharmacological therapy has an evidence base that would justify its use as an alternative to AP drugs. |
| April 2005 | US Food and Drug Administration [6] | Meta-analysis of 17 RCT involving risperidone, olanzapine, aripiprazole and quetiapine for people with dementia | 15 trials showed increased death rate for those on active comparator N=5106. Death rate 1.6-1.7 higher in active group. Cause of death mostly cardiac or infective eg pneumonia. | Increased risk of death for all atypical AP, suggesting the effect is intrinsic to function, not an epiphenomenon of associated receptor affinities. FDA planned to include a black box warning. Also considered the risk to pertain to conventional AP drugs from the database reviews. |
| 2005 | De Deyn *et al.* 2005 [74] | Meta-analysis of 3 risperidone RCT [14,16,17] | Increased incidence of CVAEs but not of death | Vascular risk factors in those with CVAEs. No clear relationship with orthostatic hypotension. |
| 2005 | Schneider *et al.* 2005 [7] | Meta-analysis of 15 RCT, 9 of which were unpublished N=3353 active comparator, N=1757 placebo | Death in drug group 3.5%, in placebo group 2.3%. OR 1.54 (95%CI 1.06-2.23), p=0.02. No differential risk for drug, severity or diagnosis | |

The UK Committee on Safety of Medicines warning in 2004[8], Royal College of Psychiatrist Guidelines[73] and initial US Food and Drug Administration statement focused on the increased risk of CVAEs with risperidone. Physicians were advised not to prescribe risperidone and olanzapine for BPSD. In the Royal College of Psychiatrists' Guidelines, clinical situations where the benefit may outweigh the risk were discussed, for example, moderate to severe BPSD in the presence of medication. A range of alternative medications were outlined, including haloperidol, although it was noted that there was little evidence for some of these alternatives. Non-pharmacological treatments were emphasised in the Guidelines, although this position was moderated somewhat in the subsequent College update in the light of the limited evidence-base for non-pharmacological treatments[22].

By contrast with the more widespread findings about increased CVAEs, the Eli Lilly olanzapine meta-analysis also suggested an increased mortality rate in those treated with olanzapine compared with placebo[5]. In this analysis there was no significant difference between olanzapine and risperidone mortality rates. The risperidone meta-analysis of three trials did not find a significant increase in risk of death[74]. The meta-analysis of Schneider *et al.,* 2005, including five risperidone trials, did not find any atypical drug (aripiprazole, olanzapine, risperidone or quetiapine) to have a significant OR of death individually, but in the aggregated data there was evidence for an increased OR of death[7].

The significance of the CVAEs as reported in the meta-analyses of the drug companies and the regulatory authorities has been questioned. The CVAEs included stroke but also TIAs and other poorly defined events. The risperidone RCTs were not controlled with regard to vascular risk factors. Subjects with CVAEs frequently had significant vascular risk factors, for example previous stroke or atrial fibrillation. Other authors questioned the acceptance of meta-analyses by drug companies and regulatory authorities when actual data could not be reviewed by researchers, nor the methodology fully critiqued[62].

The most satisfactory meta-analysis of risk of death to date has been published by Schneider and colleagues, 2005[7]. Their meta-analysis covered 15 atypical antipsychotic RCTS (9 of which were unpublished). The total number of subjects was 3353 for the active drug and 1757 for placebo. The Odds Ratio of death was 1.54 (95% CI 1.06-2.23 p=0.02). The analysis did not show a differential effect for individual drugs, severity or diagnosis.

Concern has mostly focused on the risk associated with antipsychotic use in those with dementia. Pharmaceutical company meta-analyses have not raised concerns about the risks in other elderly groups, for example those with schizophrenia or schizoaffective disorder (written communication with Eli Lilly[36]). It is likely however that those subjects were not new users of antipsychotics and possibly had been exposed to antipsychotic medication over many years. Thus they may represent a group of survivors who differ from antipsychotic naïve elderly subjects. The naïve elderly who commence an antipsychotic drug for indications apart from dementia may still be at risk due to age-related reduction in neurochemical transmission.

Review of the mechanism of drug approval and post-marketing assessment of safety may be advisable[75]. Post-marketing surveillance is not systematic and relies on reporting of adverse events. Regulatory bodies require evidence of efficacy from drug trials with relatively small numbers of subjects over brief time periods. The increased risk of cardiovascular disease with Cox-2 inhibitors, established using retrospective cohort database reviews, was detected five years after their introduction. Drugs are often used "off-label", that is, not for their approved indication. Studies done for regulatory approval may not have established safety in these heterogenous populations. Ray and Stein, 2006, propose the

development of an independent regulatory body to conduct post-marketing studies and improve the communication of drug information on the product information sheet[75].

## 1.4.2 Observational studies

Cognitive and functional decline, as well as increased mortality, occur in patients with psychosis in AD without antipsychotic use. Hallucinations, but not delusions, were associated with increased mortality in AD even when use of antipsychotic medication was controlled[76]. Whether medication is an independent contributor to decline and death has been explored in a number of studies. In a cross-sectional study with longitudinal follow-up, psychosis in AD was a predictor of functional decline and institutionalisation even when the effects of medication were adjusted[77]. The use of antipsychotic medication (n=16) was associated with functional decline and of sedative/hypnotics (n=11) with death[77]. Another small longitudinal study found that antipsychotic medication and severity of persecutory ideas were independently associated with a greater rate of cognitive decline[78]. In this study there was no correlation between rate of cognitive decline and antipsychotic drug dose. Significant cognitive decline was demonstrated in the quetiapine arm of a recent RCT[66]. Confounding variables should be reduced by the randomisation in this study.

Suh *et al.* found one year survival better for residents in a "semi-hospitalised, long-term care nursing home" on antipsychotic medication than those not on an antipsychotic even when adjusted for age, dementia severity and some medical conditions (Relative Risk 1.28 95% Confidence Interval, 1.134-1.44)[79]. However, those on antipsychotic medications were prevalent users and the group may have represented antipsychotic survivors. In an analogous finding, patients with Lewy Body Dementia who demonstrated neuroleptic (antipsychotic) sensitivity had a reduced mean survival time[80]. However, those who were exposed to neuroleptic medication but did not display sensitivity had a longer mean survival than those who had never been exposed, thus demonstrating that a survival bias may exist at least for Lewy Body Dementia.

## 1.4.3 Retrospective cohort reviews

The seven recent retrospective cohort reviews are summarised in Table 3, beginning on the following page.

Death was one of the outcome measures in four studies[9,28,81,82]. Two studies[9,28] reviewed all-cause mortality, while the outcome measure for the study by Ray *et al.* was sudden cardiac death[81]. The main outcome measure in the fourth study was admission for ventricular arrhythmias or cardiac arrest, but all cause mortality was also assessed[82]. Ray argued in a subsequent paper, that specificity of cause of death increased confidence that a drug effect was genuine[32]. However, in his 2001 study, assessment of a death as a sudden cardiac death was an arduous process. They were unable to obtain records for 33% of the sample and the records were incomplete on a further 18% of deaths. Thus in samples where autopsy confirmation is not available, all-cause mortality may be a practical option compared with an outcome of a specific type of death. In the FDA meta-analysis, deaths were related to cardiac causes or infection, for example, pneumonia[6]. Therefore a single cause for death as an outcome measure may not be appropriate.

*Table 3. Retrospective cohort studies*

| Author and year | Data and design | Statistical method | Result |
|---|---|---|---|
| Ray *et al.* 2001 | Tennessee Medicaid database, 1988-1993, 15-84 years. 25% 65 years or older. Only conventional AP studied. Prevalent users. Moderate dose AP, low dose AP, AP in previous year but not currently and no AP cohort not in RACF, censored death, stop using AP, end of study. Sudden cardiac death in community, complex definition of cardiac death, total subjects (including non-AP users) 481 744 | Multivariate rate ratios from Poisson regression models. Multiple covariates. | Moderate dose AP users had increase sudden cardiac deathrate ratio 2.39 (95% CI 1.77-3.22). Increased risk for those with severe cardiovascular disease, older and for females. Moderate haloperidol users 1.90, thioridazine users 3.19, chlorpromazine users 3.64, and thiothixene users 4.23. |
| Hennessy *et al.* 2002 [82] | US Medicaid database, 1993-1996, adult and elderly subjects diagnosed with schizophrenia and received clozapine, haloperidol, risperidone or thioridazine. Cardiac arrest, ventricular arrhythmia and all cause mortality. Glaucoma and psoriasis patients as reference groups. prevalent users | Multivariate Cox regression. Multiple medical covariates. Analysis using each reference and with haloperidol subjects as reference | The RR was significant for haloperidol, risperidone and thioridazine with the two medical reference groups for death and cardiac arrest and ventricular arrhythmias. Only risperidone was significant in the analysis using haloperidol as the reference group: cardiac arrest and ventricular arrhythmia risperidone RR 1.5 (95%CI 1.1-2.1), all cause mortality, risperidone RR 1.4 (95% CI 1.1-1.9) |
| Nasrallah *et al.* 2004 | Veterans Affairs Medical Centre, 1998 and 1999 65years and older, prevalent users, total subjects 1553. | $X^2$ test, no covariates in the model | Haloperidol users (N=299) 21.4% died, Risperidone or olanzapine users (N=1254) 4.75% died |
| Herrmann *et al.* 2004 | Ontario database, 1997-2002, Over 65 years all subjects not just dementia, incident typical AP, risperidone, and olanzapine users, at least two prescriptions. Follow up ended at hospital admission for stroke, exposure to another study medication, discontinuation of AP, death or end of study period. Total subjects 11 400 | Cox regression, unadjusted and adjusted for multiple covariates, typical AP used as reference. Number of different drugs in year before | Olanzapine RR1.1(95CI 0.5-2.3), risperidone RR1.4 (95 CI 0.7-2.8) |

| | | | |
|---|---|---|---|
| Gill *et al.* 2005 | Ontario database, 1997-2002, dementia, 65 years and older admission to hospital with stroke, Exclude TIAs. No AP use for I year, Censored if admitted with stroke, stopped taking medication, started another study drug, died or study ended. Subjects 32 710. | Atypical vs. conventional, but sub-analyses by individual atypical, Cox regression, include number of different drugs I year before. Multiple medical conditions as covariates | No sig increase in risk of ischaemic stroke for atypical (risperidone, olanzapine and quetiapine) vs. conventional AP users |
| Wang *et al.* 2005 | Pennsylvania Pharmaceutical and Medicare database, 65 or older, 1994-2003, dementia and non dementia, incident users, typical vs. atypical antipsychotic users, subjects 22 890. | Mortality rates and multivariate Cox models, propensity score adjustment, Cox regression up to 180 days, <40 days, 40-79 days, analysis presence or absence of dementia | Conventional AP higher RR of death at all time intervals, for example <180 days RR 1.37 (95% CI 1.27-1.49), <40 days, RR 1.56 (95% CI 1.37-1.78), higher RR for conventionals during the first 40 days after initial dispensing |
| Finkel *et al.*2005 | Medicaid 1999-2002, Dementia, 60 years or older, CVE hospital admission within three months of new risperidone, olanzapine, quetiapine, ziprasidone, haloperidol or BZDP dispensing, 6months AP naïve. Excluded if used more than one study drug, Included code for TIA in analysis. Subjects 18 897 | $X^2$ test, Logistic regression. Multiple medical conditions as covariates. Adjusted for days of medication use. | No sig difference risperidone, olanzapine and quetiapine. Atypicals not higher than haloperidol or BZDP. Sig predictors of CVAE were previous CVAE, AF, % days medication available in the follow up period. Lower rate of CVAE than RCTs[16] but younger patients and only CVAEs leading to hospitalisation in this study. BZDP population differed on several measures, may not have been adequately adjusted |

Two of these studies used non-antipsychotic users as a reference group[81,82]. This is problematic as the groups may differ on diagnostic as well as life style variables, for example smoking and obesity. The second of these studies also compared relative risk of death for three antipsychotic groups (clozapine, risperidone and thioridazine) against haloperidol[82]. In this study, the relative risk of death for the risperidone group was significantly higher than for haloperidol subjects. The authors postulated that frailer patients were dispensed risperidone rather than the other antipsychotic drugs.

Prevalent users were subjects in three of these studies[28,81,82]. The preference for incident user designs has emerged in recent years in the light of conflicting results from database reviews when compared with prospective RCTs, for example, the benefit of hormone replacement therapy. There were non-elderly subjects in two studies[81,82], although results for the elderly subjects were reported separately in the study of Ray *et al.*[81]. None of these studies used a dementia cohort, although Wang *et al.* performed a sub-analysis of those with dementia in their cohort[9]. Conventional antipsychotic drugs and clozapine were examined in two studies[81,82]. Wang *et al.* 2005 aggregated all atypical antipsychotic drugs and compared them with all conventional antipsychotic drugs[9]. As haloperidol is used for terminal agitation and delirium, the use of aggregated conventional antipsychotic data may bias results of the conventional antipsychotic group toward death. Thus, a sub-group analysis of the conventional data may help to establish whether increased risk of death associated with conventional AP medication is influenced by haloperidol's broader use in conditions, which of themselves, increase the risk of death.

Ray *et al.* reported those taking doses greater than 100mg of thioridazine at greater risk (rate ratio 2.39 (95% CI 1.77-3.22)) compared with non users[81]. Individual drug results were: haloperidol rate ratio 1.90 (95% CI, 1.10-3.30), thioridazine rate ratio 3.19 (95% CI, 1.32-7.68), chlorpromazine rate ratio 3.64 (95% CI, 1.36-9.74) and thiothixene rate ratio 4.23 (95% CI, 2.00-8.91). Hennessy *et al.* found that the rate of cardiac arrest and ventricular arrhythmia was higher in patients with schizophrenia using antipsychotic medication. They were unable to differentiate whether the disease or the antipsychotic drugs were causally related to this increased risk[82]. In a further analysis, clozapine, risperidone and thioridazine were compared with haloperidol in a multivariate Cox regression model. In this latter analysis, only risperidone had a significantly increased relative risk (RR) for cardiac arrest and ventricular arrhythmia and death when compared with haloperidol. Nasrallah *et al,* 2004 reported 21% of the haloperidol group died, whilst only 4.75% of the olanzapine and risperidone group died[28].

In the study of Wang *et al*., Cox regression models were used, comparing the risk of death at four time intervals[9]. Adjustments were made for many medical covariates in the final model, including an adjustment for physician choice in drug prescribing. Conventional antipsychotic subjects compared with atypical antipsychotic users had a significantly increased risk of death at all time intervals. The RR up to 180 days was 1.37 (95% CI, 1.27-1.49). The RR was 1.56 (95% CI, 1.37-1.78) in the analysis to 40 days. They found an increased RR with higher doses of conventional medication.

However, in this study there were significant differences between the atypical and conventional antipsychotic groups with regard to cancer diagnoses, dementia and use of antidepressants. Whilst these features were adjusted in the final model, it may be that other real differences existed and for which there was no adjustment. The largest methodological concern was that there was no measure of the persistence of drug dispensing, nor of the commencement of a second study drug. Thus after initial date of dispensing, the varying time periods and death were the only points at which the subjects were censored. Apparently the

aim of this design was to emulate an intention to treat analysis of a RCT. Ray discussed the benefits and limitations of this approach in his editorial[32].

Admission for stroke or transient ischaemic attacks (TIAs) were the outcome measures in three studies[10,29,35]. One of these studies was methodologically elegant[10], using incident user models and adjusting for multiple medical diseases and overall medical comorbidity[27].

Two studies used aggregated conventional antipsychotic subjects[10,35]. In contrast the third study assessed cohorts of three atypical antipsychotic drugs, haloperidol and aggregated benzodiazepine drugs[29]. Benzodiazepines are often prescribed as hypnotic medication to the elderly and, as subjects on two study drugs were censored, the study design would have excluded many potential subjects. In addition, the group of elderly dispensed benzodiazepine drugs may differ from those dispensed antipsychotic drugs in diagnoses. Two studies used only dementia cohorts[10,29] and the third included all incident subjects dispensed an antipsychotic drug over 65 years[35]. The latter trial did not report adjusting the regression model for the diagnosis of dementia[35].

In the study by Herrmann *et al.,* Cox regression models, adjusted for medical comorbidity, did not reveal a significant increase in risk ratio for olanzapine 1.1 (95% CI, 0.5-2.3) or risperidone 1.4 (95% CI, 0.7-2.8)[35]. In the study by Gill *et al.*, there was no significant increase in the incidence of admission for stroke for atypical compared with typical antipsychotic drug users[10]. As mentioned by the authors, ascertainment bias may have influenced the results, as some subjects with strokes may not go to hospital. The third study found no significant increase in admissions for stroke and TIA among the olanzapine or quetiapine subjects, compared with risperidone subjects[29]. However there was evidence of increased stroke admissions for haloperidol subjects compared with the risperidone cohort. There was also a significant increase for the benzodiazepine group compared with the risperidone cohort, however it may not be appropriate to compared these two groups. Risk factors for stroke were important predictive variables in this study, for example past history of stroke or atrial fibrillation. Perhaps future RCTs should stratify subjects according to vascular risk factors.

The studies by Herrmann *et al.* and Gill *et al.* used similar methodology[10,35]. Subjects were censored on admission to hospital for stroke, at death, on discontinuation of the drug, starting a second study drug, or at the end of the study. This approach, more than any of the other designs, linked antipsychotic dispensing, and by implication consumption, with the outcome measure. The "fixed dose" model of Wang *et al.*, where continuation of dispensing is not assessed, is not logically consistent with the hypothesis that drug consumption is related to an adverse event. Finkel *et al.* adjusted their model for "days of medication use" but from the methodology it would appear that those dispensed one prescription, who failed to fill a second prescription were still included in the analysis[29]. In one study, the choice of ICD9 codes included the code for TIAs (ICD 9 435.xx)[29]. Whilst this mirrors concerns raised in the risperidone trials, TIAs do not have the same diagnostic certainty as stroke diagnoses and the ICD-9 code for TIAs were not included in other studies[10].

### 1.4.4 Retrospective case control reviews

A case control study asserted that conventional antipsychotic medication, but not atypical antipsychotic medication, was associated with an increase in admissions for ventricular arrhythmias and cardiac arrests in nursing home residents[83]. The cases were more likely to have significant heart disease and the controls were more likely to have dementia. The controls were those admitted to hospital with four types of gastrointestinal bleeding, septicaemia and influenza. The Odds Ratio for conventional antipsychotics to be associated

with admission for ventricular arrhythmias and cardiac arrests, compared with atypical antipsychotic medication, was 2.13 (95% CI 1.27-3.60). However, by corollary, atypical antipsychotic medications (71% risperidone) were associated with an increased OR for gastrointestinal bleeding, septicaemia and influenza. Risperidone use has been associated with nose bleeds[84]. The authors postulated that risperidone, a potent 5-$HT_2$A receptor antagonist, may act in a similar way to sarpogrelate, another potent 5-$HT_2$A receptor antagonist. Sarpogrelate improves coronary microvascularisation by reducing platelet aggregation and vasoconstrictor release from platelets.

A three-fold increase in risk for sudden cardiac death was found in current users of conventional antipsychotic medication[85]. The risk was greatest for those using a butyrophenone, haloperidol or pipamperone (the latter not available in Australia), and in the first 90 days after dispensing. The risk was higher in males. Another case control study demonstrated an increased risk of idiopathic venous thrombosis in conventional antipsychotic users[86]. The association was most marked for low potency sedating antipsychotic drugs. The risk was highest in the first few months of treatment. These authors hypothesised that conventional antipsychotic drugs may enhance platelet aggregation or that sedation contributed to venous stasis. These last two studies only assessed conventional antipsychotic use as the atypical antipsychotic medications were not widely available at that time.

## 1.5 OTHER MEDICATION OPTIONS FOR THE TREATMENT OF BPSD

### 1.5.1 Carbamazepine and valproate

Carbamazepine was assessed in a six week RCT in 51 nursing home patients with AD[23]. The modal dose of carbamazepine was 304mg/day, with the average blood level 5.3 micrograms/ml. There were some methodological weaknesses in this study, in particular, the physician adjusting the medication was not blinded. There was a significant improvement on Clinical Global Impression of Change (CGI-C)[87] favouring subjects on active treatment (77% vs. 21%). Factor analysis of the BPRS results showed that agitation and hostility improved significantly. However, more adverse events occurred with carbamazepine than with placebo (16/27 vs. 7/24). Carbamazepine's tendency to interact with other medications limits its usefulness in the elderly. A small RCT (N=21) failed to detect a treatment difference (Olin *et al.*[88], cited in Sink *et al.*[89]).

A Cochrane Database review of preparations of valproate for treatment of agitation in dementia concluded that the evidence of efficacy in this area should be considered preliminary[26]. Porsteinsson and colleagues[25], randomised 56 nursing home residents with dementia and agitation to divalproex sodium or placebo. The mean daily dose was 826mg per day, with an average level of 45micrograms/day. The physician adjusting the medication was not blinded. There was evidence for the efficacy of valproate on the BPRS in a model adjusted for covariates (p=0.05), but no evidence for efficacy on the CGI rating. There were significantly more side effects in the treated group. The strength of this study, like the earlier carbamazepine study by Tariot *et al.* 1998[23], was the inclusion of medically frail patients.

A large trial (N=172) of divalproex sodium for "manic" symptoms (agitation, irritability, lability, resistive behaviour and sleep/wake cycle disturbance) in AD and vascular dementia was terminated prematurely due to the high discontinuation rate and number of adverse events in the treated group[24]. There was rapid titration of the divalproex sodium to 20mg/kg-30mg/kg per day (the dosing recommended in treatment of mania in adults) over 6

weeks. There was no evidence of efficacy on a mania rating scale, although the total CMAI and the verbal agitation sub-scale demonstrated an effect for divalproex sodium. Discontinuation rate for active drug compared with placebo was 54% compared with 29%. There were 5 deaths in the treated group and one in the placebo group. Whilst this was not significant in this trial, if other trials existed, it is possible that a meta-analysis may indicate an increased risk of death in a manner analogous to the process with atypical antipsychotic medication. The major side effect was somnolence, more marked above doses of 15mg/kg/day. One patient developed thrombocytopaenia, one had raised liver function tests, one had raise creatinine and potassium levels and one displayed increased urea. All these abnormalities were corrected after cessation of the divalproex sodium.

A further small cross-over trial of valproate on inpatients did not report benefit on the primary outcome measures[90]. However, the treatment period was only 3 weeks and the washout period of one week may not allow any neuroreceptor changes to return to drug naïve state. In contrast to the previous study, valproate 240mg twice daily, with a mean blood level of 40 microg/ml, was well tolerated.

In summary, there is some evidence for efficacy for carbamazepine in treating agitation in AD[23], however, these findings have not been replicated and the tendency for carbamazepine to interact with other medication makes use of this drug in the elderly not without risk. There was some evidence of efficacy for valproate on BPRS in an adjusted model[25] however, other studies did not show evidence of efficacy on the primary outcome models. It is possible that "mania" in AD is not a valid construct and that measuring agitation with validated measures such as the CMAI may be more appropriate. The large study of divalproex sodium also highlighted the risks associated with rapid titration of the drug to achieve dosing regimes consistent with treatment of mania in adults. Valproate is often used at lower dosages in the treatment of BPSD, although there is no evidence from RCTs for this clinical approach.

### 1.5.2 Cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonist

An extensive review of cholinesterase inhibitors studies is beyond the scope of this literature review. RCTs of cholinesterase inhibitors in Alzheimer's Disease have demonstrated a delay of 6 to 9 months in cognitive decline for the actively treated subjects compared with those on placebo. Those trials have been reviewed[91]. More recent trials have included scales to assess Activities of Daily Living (ADLs) and non-cognitive features.

A meta-analysis of 29 trials demonstrated a modest but significant improvement on the Neuropsychiatric Inventory (NPI) and a non-significant trend toward improvement on the Alzheimer's Disease Assessment Scale-noncognitive (ADAS-noncog) subscale for subjects taking cholinesterase inhibitors. The authors criticised the ADAS-noncog for not including items assessing aggression or agitation. The major limitation of this study was that the original trials were constructed to assess cognitive effects of the drugs and subjects may not have had significant neuropsychiatric symptoms.

A trial of rivastigmine in patients with mild to moderate Dementia with Lewy Bodies found that treated subjects were less apathetic and anxious and had fewer delusions[92]. However, 18/59 rivastigmine subjects and 10/61 placebo subjects withdrew. Thus the intention to treat and last observation carried forward analyses for NPI-4 and NPI-10 scores were not significant.

In a secondary analysis of a galantamine RCT, Cummings *et al.* reported that subjects on the active drug who were asymptomatic at baseline had a reduction in the emergence of new symptoms compared with placebo[93]. There was also a significant reduction in caregiver distress as measured by the Neuropsychiatric Inventory Measure of Caregiver Distress. A post-hoc meta-analysis of three galantamine trials demonstrated a modest treatment effect for galantamine on the following behaviours: agitation/aggression, anxiety, disinhibition and aberrant motor behaviour[94].

Memantine, an N-methyl-D-aspartate receptor antagonist, was found to reduce total NPI scores and scores for aggression/agitation in a meta-analysis of two RCTs of subjects with moderate to severe Alzheimer's disease[95].

### 1.5.3 Antidepressant medication

Studies assessing the use of serotinergic antidepressants in BPSD have mostly found no significant benefit[21,96]. One study of citalopram was 17 days long, in hospitalised patients[53]. The study by Lyketsos *et al.* found sertraline an effective treatment for depression in AD[97]. Sertraline, however, did not provide a reduction in NPI scores in those whose depression failed to respond to the antidepressant medication. The reduction in NPI scores in responders may have been mediated by the treatment of depression and thus the study does not support the use of sertraline to treat neuropsychiatric conditions apart from depression. The use of antidepressant medication in dementia has been the subject of a Cochrane Database Review[98].

## 1.6 POSSIBLE MECHANISMS OF ANTIPSYCHOTIC DRUG TOXICITY

This area has been summarised in previous reports[99]. Recent meta-analyses have suggested that deaths have been caused by cerebrovascular events, cardiac events and infections, such as, pneumonia[5,6].

### 1.6.1 Cardiac events

Many antipsychotic medications prolong the QTc interval (the length of the QT interval on the electrocardiogram when adjusted for rate). Drug regulatory authorities consider QTc prolongation to be a marker for the tendency of a drug to cause ventricular arrhythmias. Thioridazine and droperidol have been associated with QTc prolongation[100]. Thus, in Australia thioridazine has restricted indications for prescribing and in the USA droperidol has a black box warning regarding this issue. Amisulpride can cause QTc prolongation according to the prescribing information. In animal models, haloperidol, risperidone, sertindole, clozapine and olanzapine all produced a dose dependent QTc prolongation[101].

Other drugs have been noted to cause QTc prolongation, for example, lithium and tricyclic antidepressants[100]. The risk of QTc prolongation may increase with low serum potassium, female gender, pre-existing cardiac disease, other drugs that prolong the QTc interval and age. Idiopathic venous thrombosis has been associated with conventional antipsychotic drugs, especially low potency medications[86]. Pulmonary thromboembolism may be difficult to differentiate from sudden cardiac death without an autopsy.

### 1.6.2 Cerebrovascular adverse events

RCTs for atypical antipsychotic drugs in those with dementia have demonstrated a significant increase in cerebrovascular adverse events. Risperidone, quetiapine and other antipsychotic

medications are associated with orthostatic hypotension (that is, a fall in blood pressure when moving from lying to standing). The consequences of orthostatic hypotension may include a watershed infarct or falls. There have been some case reports of bleeding with risperidone and speculation about the effect of 5-$HT_2$A receptor antagonism on platelet aggregation[84].

### 1.6.3 Pneumonia

A high proportion of deaths in dementia is attributable to pneumonia. Antipsychotic drugs, male gender, silent brain infarction in the basal ganglia and severity of dementia were independently associated with aspiration pneumonia in ambulatory subjects with AD [102]. In this study, latency of swallow was increased three hours after ingestion of antipsychotic medication. The latency of swallowing was not increased after the ingestion of benzodiazepine medication and benzodiazepine medications were not associated with aspiration pneumonia in this study. L-dopa has been reported to improve swallowing function (cited in Wada *et al.* [102]).

### 1.6.4 Extra-pyramidal side effects (EPSE)

Dopamine blockade in the nigrostriatum produces EPSE, such as dystonic reaction, tremor and increased muscle tone. Akathisia, a subjective or objective sense of restlessness, may also be a side effect of antipsychotic medication. In the elderly, there is loss of dopaminergic transmission even in those without preclinical Parkinson's disease, and hence the elderly are particularly susceptible to these side effects. Atypical antipsychotic medications are less likely to cause EPSE compared with conventional antipsychotic medication. The development of EPSE may lead to falls and swallowing difficulties.

Tardive dyskinesia is a potentially irreversible movement disorder usually caused by exposure to antipsychotic medication. For antipsychotic naïve subjects over 55 years, the cumulative rate of tardive dyskinesia was 25%, 34% and 53% after 1, 2 and 3 years of treatment[103]. Tardive dyskinesia can impair swallowing and, in extreme cases, breathing. It is unlikely to contribute to the mortality rates seen in short-term RCTs.

In a retrospective review, 57% of patients with Dementia with Lewy Bodies experienced neuroleptic (antipsychotic) sensitivity, resulting in increased mortality rates compared with the non-exposed group[80]. Dementia with Lewy Bodies has been reported as the second most common cause of dementia in hospital autopsy studies and may be found on autopsy in patients diagnosed with AD[104]. Thus some antipsychotic associated deaths may pertain to antipsychotic exposure in those with Dementia with Lewy Bodies.

### 1.6.5 Sedation, falls and anticholinergic activity

Sedation may be associated with falls, aspiration pneumonia and venous thrombosis. Antipsychotic drug use in nursing home residents was associated with an increased risk of falling[105]. The mechanism for increased risk of falls may pertain to EPSE, sedation or orthostatic hypotension. Wandering in dementia may be a confounding factor leading to both increased risk of falls and antipsychotic medication use[106]. Drugs with anticholinergic activity can increase confusion. Conventional antipsychotic drugs such as chlorpromazine and thioridazine have prominent anticholinergic side effects. Clozapine has the has the most pronounced anticholinergic activity of the atypical drugs.

### 1.6.6 Neuropathological changes

A review of animal and in vitro studies in this area is beyond the scope of this report. There are some preliminary findings that suggest antipsychotic drugs, via their dopamine blocking action, down-regulate brain derived neurotrophic factor which in turn results in excess tau

formation. In a small observational study of those with Dementia with Lewy bodies, antipsychotic use was associated with increased neurofibrillary tangles[107]. These subjects were not randomised. It may be that neurofibrillary tangles are causally related to psychotic symptoms and hence the medication is an epiphenomenon. An increase in tissue transglutamase, a marker for cell apoptosis, was found in the cerebrospinal fluid of subjects taking antipsychotic medication compared with those not using antipsychotic drugs in demented and non-demented subjects[108]. This was an observational study and it is impossible to exclude behavioural disturbance as a confounding variable. However, the contention that antipsychotics may be neurotoxic is supported by in vitro studies. In neuronal cell culture, cell viability was decreased by perphenazine (87%) clozapine (43%) and haloperidol (34%) (cited in Bonelli *et al.*[108]).

### Other side effects

Atypical antipsychotic medications have been associated with weight gain, dyslipidaemia and glucose intolerance. Whilst these concerns are relevant to the management of patients who remain on these drugs in the longer term, they would not explain the findings of the atypical antipsychotic RCTs.

## 1.7 METHODOLOGICAL ISSUES

A prevalent cohort is a cohort of survivors, with those encountering the adverse events having died or withdrawn from treatment. Observational studies enrolling prevalent users can lead to an under-ascertainment of adverse events occurring early in treatment[109]. The incident user study design synchronises the enrolment of subjects with commencement of drug exposure[32]. Despite the growing preference for incident user designs in observational database studies, RCTs do not necessarily report whether subjects have had previous exposure to antipsychotic medication.

In prospective clinical trials, subjects with significant medical comorbidities are often excluded. This limits generalisability of the trial results, particularly in older populations where comorbid disease is common. The Charlson index is a weighted index of 19 conditions designed to predict death from comorbid disease[110]. In her analysis of 10 year survival in breast cancer patients, only age and the comorbidity index were significant predictors of death from medical comorbidity, that is, non-cancer deaths[110]. This index was designed for use in clinical studies rather than database reviews. In large databases, the accuracy and completeness of diagnostic data may limit the application of indices such as the Charlson Index.

In large database studies controlling for confounding variables is difficult. Schneeweiss *et al.,* 2001, compared four comorbidity scores based on the International Classification of Diseases, Ninth Revision, (ICD-9), two medication based scores and the total number of distinct medications in the year before entry to the trial[27]. The different models were assessed using a logistic regression and *c* statistics, that is, the area under the receiver operating characteristic curve. One ICD-9 based index, namely, the Romano adaptation of the Charlson Index, with age and gender added, had a *c* statistic of 0.771 in predicting mortality. This represented an 11.7% improvement over a model using age and gender alone. The *c* statistic for predicting mortality obtained by using the number of distinct drugs, age and gender, was 0.745. Overall, the best predictor of mortality was obtained using age, gender, medication based score or total number of drugs, and the Romano Index ($c$=0.783). Improving the *c* statistic from 0.745 to 0.783 represents an improvement of less than 8% in the predictive value. Whether it is worth purchasing and processing the diagnostic data depends on the specific study. The number of distinct medications received in the baseline

year performed well as a predictor of mortality. In addition, the number of distinct medications received during the baseline year was the best predictor of total expenditure and expenditure on physician services.

Ray suggested that observational studies of overall mortality are subject to biases of "channelling" (selection of patients for specific therapies for reasons that are hard to measure)[32]. He argued that specificity of effect is an important feature in implying causality. Thus he considered observational studies that examined individual causes of death to be superior to those reporting all-cause mortality. In his own study examining sudden cardiac death in antipsychotic users[81], it was hard to define accurately this type of death and many deaths were excluded due to insufficient information. If a drug contributed to a specific type of death, studying all-cause mortality may increase the chance of a negative finding. A true positive finding would occur if the effect was large enough to rise above the data "noise" of other deaths in the exposed and non-exposed groups.

Arguments for and against fixed drug exposure versus variable drug exposure models were discussed by Ray[32]. With a variable model, serious illness may lead a doctor to remove a patient from medication, leading to a false negative association. To avoid this, some have recommended emulating the intention to treat analysis of randomised, controlled trials. This is done by determining drug exposure at a point, for example first dispensing of a drug, and considering the exposure as fixed until the end point is measured. Several studies have followed this concept of fixed exposure[9]. However, these theoretical concerns are not supported in clinical practice, where severely ill patients are often put on antipsychotic medication[30]. Indeed the specific bias raised by Ray could be tested by reviewing risk of death several months after discontinuation. A fall in risk would not support the hypothesis.

A fundamental hypothesis in database reviews is that consumption of the drug is related to an outcome, usually adverse. Considering drug exposure as fixed does not allow for subjects to stop medication or start others. Real medication effects may be undetected because subjects no longer consuming the drug are included in the drug group. In addition, the comparison with the intention to treat design of RCTs is not robust. In RCTs this design serves primarily to limit an untrue positive result by including in the analysis those who fail to gain benefit or to tolerate the medication and then withdraw. It also acts as a safeguard against attempts to unblind the trial. In an observational study, the subjects are not randomised and the outcome is usually adverse.

Studies that compare drugs with similar indications may provide some defence against confounding variables[32]. The aggregation of haloperidol, and perhaps chlorpromazine, with other conventional drugs may bias the conventional group towards death because haloperidol is used in delirium and palliative care[30]. The off-licence use of risperidone and olanzapine for delirium may similarly bias the drugs toward death. Antipsychotic non-users differ on important points with users and hence are not adequate reference groups. Even within dementia, those for whom a physician would prescribe an antipsychotic medication may differ from those for whom no-one prescribed the drugs. Thus cholinesterase inhibitor users, a dementia cohort, are not an appropriate group to compare with dementia sufferers dispensed antipsychotic drugs. The most valid comparison is among drugs used in a similar manner, for example, olanzapine and risperidone.

## 1.8 SUMMARY

The evidence for efficacy of antipsychotic medication in treatment of aggression and agitation in BPSD rests on several trials[14-17,47]. The evidence for efficacy in treatment of

psychosis in dementia is more restricted[14-16]. There have been a number of trials that did not demonstrate efficacy on the primary outcome measures[17-21]. The positive trials were more likely to have institutionalised subjects with severe dementia and to have used scales that measured aggression and agitation. Some of the trials with negative results had high placebo response rates, possibly indicating that BPSD may be transitory or that non-specific attention may settle symptoms in some individuals. Nursing home residents who had been on antipsychotic medication for three months and whose symptoms settled (NPI score <15) were able to be withdrawn from medication without deterioration in behaviour[57]. Risperidone has the broadest evidence-base of support[14,16,17]. There is one study which unequivocally supports the efficacy of olanzapine in BPSD[15].

There is evidence from RCTs that all atypical antipsychotic medications are associated with an increased RR of death[7]. The database review by Wang *et al.* suggested that conventional antipsychotic drugs were associated with an increased risk of death compared with atypical antipsychotic subjects. However, the subjects in these two groups differed on important features and the adjusted model may not have adequately compensated for all differences[9]. In particular, the inclusion of haloperidol in the conventional group may have biased the results of this group toward death. Earlier studies have suggested that there is an increased risk of death for those using antipsychotic medication [81,82], however, antipsychotic non-users are probably not an appropriate reference group. The US FDA meta-analysis of RCTs found that the increase in deaths were due to cardiac causes or infections, such as pneumonia [6]. From database reviews, this agency concluded that conventional antipsychotic drugs may also be associated with increased risk of death.

Meta-analyses of RCTs suggest there is an increased incidence of stroke in the atypical antipsychotic users [4,5,8]. There is no evidence from database reviews that the risk with atypical antipsychotic medication is higher than with conventional antipsychotic drugs [10,35]. In one study, haloperidol was associated with a higher RR of admission for stroke than risperidone [29], however, the study design was not without criticism.

There is some evidence that cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists may lessen some symptoms of BPSD[111], however in many trials the primary outcome measures assessed cognitive functioning and subjects were not enrolled with significant neuropsychiatric symptoms. The evidence for carbamazepine and valproate in treatment of BPSD is best regarded as preliminary [23,26].

# 2. METHODOLOGY

Subjects were Department of Veterans' Affairs (DVA) Entitled Beneficiaries, 65 years and older on 1.1.2003. who were dispensed an antipsychotic (AP) drug, carbamazepine or valproate (C/V) in the calendar years of 2003 and 2004. The sample was divided into incident and prevalent medication recipients and analysed separately. Incident users were subjects with no dispensing of a study drug in the prior twelve months. The incident sample was further divided into two sub-samples: those subjects who had been dispensed a cholinesterase inhibitor at any point from 2001 to 2004, and those subjects who resided in an Aged Care Facility at any time in 2003 or 2004. Gender, date of birth, date of death and postcode at 1.1.2003 were extracted from the DVA administrative database.

DVA beneficiaries were either veterans or spouses of deceased veterans. DVA entitlements included pharmaceutical subsidies, no co-payments for specialist medical reviews or allied health services, and free public or private hospital admissions. DVA pension entitlements were more generous than aged pension equivalents.

Ethics approval was granted by the DVA Human Research Ethics Committee (February, 2005), the University of Sydney Human Research Ethics Committee (May, 2005) and the Australian Institute of Health and Welfare (AIHW) Ethics Committee (October, 2006). Subsequent changes to the initial study protocol were approved by the DVA Human Research Ethics Committee. Subjects were allocated a study code number. Deidentified data were used for the analysis.

## 2.1 PHARMACEUTICAL DATA

The DVA Pharmaceutical database is a claims based system covering drugs that are available under the Repatriation Pharmaceutical Benefits Scheme (RPBS). Claims for payment are originally received and processed by for payment by Medicare Australia, formerly known as the Health Insurance Commission. After payment, records are passed to DVA, where further checks are performed. Pharmaceutical dispensing occurring in the community, in residential aged care, in hospices and in private hospitals was recorded. Pharmaceutical dispensing occurring in the state funded public hospitals was not captured.

### 2.1.1 Study drug cohorts

#### 2.1.1.1 Antipsychotic (AP) drugs

The 11 AP drugs used by subjects were amisulpride, aripiprazole, chlorpromazine hydrochloride, clozapine, haloperidol, olanzapine, pericyazine, quetiapine fumarate, risperidone, thioridazine and trifluoperazine hydrochloride. Depot medications were not included.

#### 2.1.1.2 Carbamazepine and sodium valproate (C/V)

Carbamazepine and sodium valproate, two antiepileptic drugs used in treatment of mood disorders and behavioural and psychological symptoms in dementia, were included.

Dates for each dispensing for the 13 drugs in calendar years 2003 and 2004 were extracted. In addition, strength was extracted for all AP drugs. Subjects were removed from the analysis if the date of death preceded the date of last dispensing by more than seven days.

### 2.1.2 Incident or prevalent users

Analyses conducted with prevalent users underestimate adverse events occurring early in the treatment. Analysing incident user data reduces this bias[109]. The dates of dispensing of AP

and C/V for the cohort were extracted for the preceding year, 2002. The 2002 data were used to categorise subjects as either an incident or prevalent drug user. Subjects were classified as incident users if they were naïve for any AP or C/V in the 12 months prior to their first date of dispensing of an AP in 2003 or 2004. Subjects were only be entered once in the analysis. Thus, a subject from the prevalent cohort who discontinued all study medication in 2003 and then restarted a study drug after a 12 month interval, could not be entered a second time into the study as an incident subject.

Subjects who took two or more study drugs over the two year period were considered incident users for the first drug dispensed. The subjects were followed until commencement of the second drug**.** There were four points at which the data were censored: death, commencement of a second study drug, 60 days after discontinuation of a study drug, or 31.12.04. Those who were simultaneously commenced on two study drugs were classified in the mixed group. In randomised control trials, as a consession to the half life of the drug and any slower correction of homeostasis, death is potentially attributable to the study drug for 30 days after discontinuation. It was assumed that 30 days of medication was dispensed on each date of dispensing, thus 60 days allowed for consumption of dispensed medication and drug washout period.

## 2.1.3 Pharmaceutical dispensing for subjects in 2003 and 2004

Pharmaceutical databases were interrogated for dispensing of other medication during 2003 and 2004. The presence or absence of dispensing in the two year period was recorded by a "1" or a "0".

These medications were
1. Psychotropic dugs,
2. Cardiovascular drugs,
3. Drugs reflecting cardiovascular risk factors,
4. Drugs used in Parkinson's disease, excluding anticholinergic drugs
5. Anticholinergic drugs
6. Drugs used to treat tardive dyskinesia
7. Drugs used to treat epilepsy apart from carbamazepine, valproate and clonazepam

Data on the following drugs were collected with date of dispensing for 2003 and 2004:
1. Cholinesterase inhibitors
2. Morphine
3. Selective inhibitors of cyclo-oxygenase 2 (COX-2) non-steroidal anti-inflammatory drugs
2. Drugs used to treat cancers.

Drug classification was based on the Anatomical Therapeutic Classification, World Health Organisation and the Schedule of Pharmaceutical Benefits.

### 2.1.3.1 Psychotropic drugs

**Antidepressants:** amitriptyline hydrochloride, clomipramine hydrochloride, dothiepin hydrochloride, doxepin hydrochloride, imipramine hydrochloride, nortriptyline hydrochloride, trimipramine, citalopram hydrobromide, escitalopram oxalate, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, sertraline hydrochloride, tranylcypromine sulphate, phenelzine sulphate, moclobemide, mianserin hydrochloride, mirtazepine, nefazodone hydrochloride, reboxetine mesylate, venlafaxine hydrochloride.
**Benzodiazepines:** alprazolam, bromazepam, clobasam, clonazepam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam.
**Non-benzodiazepines:** zopiclone, zolpidem tartrate, buspirone hydrochloride.
**Lithium carbonate.**

**Antihistamines**: azatadine maleate, cetirizine hydrochloride, chlorpheniramine maleate, cyproheptadine hydrochloride, dexchlorpheniramine, doxylamine succinate, fexofenadine hydrochloride, loratadine, mepyramine maleate, methdilazine, pheniramine maleate, promethazine theoclate/hydrochloride, trimeprazine tartrate. Antihistamines used as antiemetics were excluded: prochlorperazine maleate (Stemetil). Antihistamines can be bought without a prescription so the data may not reflect the complete use of antihistamines.

#### 2.1.3.2 Cardiac drugs

Data regarding dispensing of cardiovascular drugs were collected in 10 categories(anti-arrhythmics, angiotensin converting enzyme inhibitors and receptor blockers, antihypertensives, antithrombotic or anticoagulant drugs, beta-blockers, calcium channel blockers, diuretics, glycosides, and vasodilators).

**Anti-arrhythmics:** disopyramide, procainamide hydrochloride, quinidine bisulphate, lignocaine hydrochloride, mexiletine hydrochloride, flecainide acetate, amiodarone hydrochloride.

**Angiotensin converting enzyme inhibitors and receptor blockers:** captopril, enalapril, quinapril, trandolapril, cilazapril, ramipril, perindopril, losartan, irbesartan, candesartan, telmisartan.

**Antihypertensives:** methyldopa, clonidine, prazosin hydrochloride, hydralazine hydrochloride, minoxidil, sodium nitroprusside.

**Antithrombotic, anticoagulant or fibrinolytic drugs:** abciximab rmc, alteplase, aprotinin, aspirin, anti-thrombin iii, clopidogrel hydrogen sulphate, dalteparin sodium, danaparoid sodium, dipyrimadole, enoxoparin sodium, eptifibatide, fondaparinux sodium, heparin calcium,/sodium, lepirudin, phenindione, reteplase, streptokinase, tenecteplase, ticlopidine hydrochloride, tirofiban, warfarin sodium.

**Beta-blockers:** alprenolol, atenolol, bisoprolol, carvedilol, esmolol, metoprolol, oxprenolol, pindolol, practolol, propranolol, sotolol, timolol.

**Calcium channel blockers:** diltiazem, felodipine, lercanidipine, nifedipine, verapamil, amiodipine

**Diuretics:** bendrofluazide, chlorthalidone, indapamide hemihydrate, bumetanide, frusemide, ethacrynic acid, spironolactone, amiloride hydrochloride, hydrochlorothiazide with amiloride hydrochloride, hydrochlorothiazide with triamterene.

**Glycosides:** digoxin.

**Vasodilators (anti-angina drugs):** glyceral trinitrate, isosorbide dinitrate, isosorbide mononitrate, nicorandil.

#### 2.1.3.3 Other drugs reflecting increased vascular risk factors

**Diabetic drugs:** all insulin preparations, acarbose, glibenclamide, gliclazide, glimepiride, glipizide, metformin, repaglinide, pioglitazone hydrochloride.

**Hypolipidaemic agents:** atorvastatin, cholestyramine, colestipol hydrochloride, ezetimibe, fluvastatin sodium, gemifibrozil, nicotinic acid, pravastatin, simvastatin.

#### 2.1.3.4 Drugs associated with Parkinson's disease and parkinsonism

**Drugs used in Parkinson's disease excluding anticholinergic drugs:** amantadine, apomorphine hydrochloride, benserazide hydrochloride:levodopa, cabergoline, carbidopa:levodopa, entacapone, pergolide mesylate, selegiline hydrochloride.

**Anticholinergic drugs:** biperiden, benzhexol hydrochloride, benztropine mesylate

**Drug used to treat tardive dyskinesia:** tetrabenazine.

#### 2.1.3.5 Anti-epileptic drugs

Anti-epileptic drugs: gabapentin, lamotrigine, levetiracetam, phenobarbitone, phenytoin, primidone, sulthiamine, tiagabine hydrochloride, NB clonazepam excluded.

#### 2.1.3.6 Cholinesterase inhibitors

Cholinesterase inhibitors: donepezil hydrochloride, galantamine hydrobromide and rivastigmine hydrogen tartrate. These drugs require a diagnosis of Alzheimer's Disease from a neurologist, psychiatrist or geriatrician to attract the subsidy from the Repatriation Pharmaceutical Benefits Scheme or the Pharmaceutical Benefits Scheme.

#### 2.1.3.7 Drugs associated with increased risk of death

**Morphine:** all morphine formulations (date of dispensing recorded).
**Coxibs:** celecoxib, rofecoxib (date of dispensing recorded).
**Anti-neoplastic drugs:** altretamine, anagrlide, bleomycin sulphate, busulphan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin hydrochloride, epirubicinin, etoposide, fludarabine phosphate, fluorouracil, flutamide, fotemustine, gefitinib, gemcitabine, goserelin acetate, idarubicinin, ifosfamide, imatinib mesylate, interferon alpha-2b, irinotecan, leuprorelin acetate, lomustine, megestrol acetate, melphalan, methotrexate, mercaptopurine, mitomycin, mitozantrone, oxaliplatin, paclitaxel, procarbazine hydrochloride, raltitrexed, rituximab, tamoxifen citrate, temozolomide, teniposide, thioguanine, thiotepa, topotecan, trastuzumab, vinblastine sulphate, vincrisitne sulphate, vindesine sulphate, vinorelbine tartrate, (date of dispensing recorded).

### 2.1.4 Measure of overall medical comorbidity

In prospective clinical trials, subjects with significant medical comorbidities are often excluded limiting their generalisability. Database reviews reflect actual clinical prescribing and include elderly subjects, those who are ill and those who receive medication for "off-licence" diagnoses. However, when analysing databases, adjustment must be made for medial illness as a confounding variable for death. Research has shown that the number of distinct medications received in the baseline year performs almost as well as the Charlson Index as a predictor of mortality[27,110].

The total number of distinct drugs dispensed in twelve months periods were calculated for all subjects at three monthly intervals (twelve months prior to 31.12.02, twelve months prior to 31.3.03, twelve months prior to 30.6.03 etc). Thus for all subjects there were at least four total scores and for some subjects there were 9 scores. (A subject that died on 1.1.03. would have total scores on 31.12.02/31.3.03/30.6.03/30.9.03). For each subject the score immediately preceding the first date of dispensing for AP or C/V drug was used as the measure of comorbidity.

## 2.2. RESIDENTIAL AGED CARE FACILITY STATUS

Dates of admission and discharge from residential care, as well as residential high and low care status, were collected. Residential status at 1.1.2003 was recorded. The study cohort was classified as either receiving AP, carbamazepine or valproate dispensing in the community, in a residential aged care facility or in part in the community and in part in a residential aged care facility.

## 2.3. PUBLIC AND PRIVATE HOSPITAL ADMISSIONS IN NSW AND ACT IN 2003 AND 2004

The study cohort was separated into state of residence by postcode at 1.1.03. Those with postcodes from 2000-2999, pertaining to residency in New South Wales (NSW) and the Australian Capital Territory (ACT) formed the cohort from which admissions for fractured

femur, and, stroke, in NSW and ACT private and public hospitals, were examined. Postcodes at 30.6.2003 were extracted and compared with the postcodes from 1.1.2003 to establish the percentage of subjects who move during a six month period. Only 28 changes of postcodes in the entire sample occurred over this time, none involving NSW or ACT.

### 2.3.1 Hospital data from public and private admissions in NSW and ACT in 2003 and 2004

The following primary diagnoses were extracted with date of admission from the NSW and ACT public and private hospital services data. Non-primary diagnoses were not extracted.

| | |
|---|---|
| Fractured femur | S7200-S729 |
| Stroke | H34.1, I60.x, I61.x, I63.x, I64.x |

## 2.4. AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE (AIHW), NATIONAL DEATH INDEX (NDI) DATA

To ascertain the certified cause(s) of death of subjects who died in 2003 or 2004, name, date of birth and date of death of subjects were submitted to the AIHW for matching with the NDI records. All possible NDI record matches for each subject were allocated a match-probability weighting by AIHW and returned to DVA (without showing the cause of death for privacy reasons). Clerical review of these matches was performed within DVA by one of the collaborators (LF). Subjects who were matched with an acceptable level of probability were then returned to AIHW for retrieval of the cause(s) of death for those subjects. Deidentified NDI records showing underlying and other cause(s) of death were then sent to the collaborators external to DVA.

## 2.5. STATISTICAL METHODS

The packages SPSS6.1.3, SPSS13.0 and STATA SE 8.0 were used for analyses.

As discussed in detail below (5.5 onwards), multivariate Cox Regression and Logistic Regression models were fit in various (sub-)samples of subjects. The general analysis strategy was as follows:

(a) all AP and C/V drug groups were enumerated and those with less than 20 subjects removed from analysis by removing those subjects from the analysis;
(b) all dichotomous covariates (e.g. sex, drug usage) were enumerated and those covariates with less than 20 clients active were ignored in the analysis.

A final model involving both the AP and C/V drug groups and the covariates, with death as the dependent variable, was then achieved by:

(c) fitting each covariate singly with the AP and C/V drug classification, and removing those covariates from further analysis that resulted in $p > 0.05$;
(d) the remaining (significant) covariates were then run together with the complete AP and C/V classification, and their partial-p values noted;
(e) those with partial-$p > 0.05$ in (d) were then omitted, and the model in (d) re-run without them, usually resulting in a final model. (Occasionally a covariate that was significant in (d) lost its significance in (e), was added to the omitted set from (d) and step (e) repeated.) All omissions were tested with deviance tests between (d) and the final model in (e);
(f) with the set of significant covariates refined in the above manner and present in subsequent modelling, the AP and C/V drug predictors were then tested and non-significant drug predictors omitted to arrive at a final model for the drug effects adjusted for significant covariates. In the Cox Regressions the AP and C/V drug

classification was fit as dichotomous indicator variables with that for olanzapine omitted, making it the reference group for resulting RRs; in the Case-Control Logistic Regressions, such omission was unnecessary as within every drug group there were subjects not exposed in the 60 days preceding their "study date" (see below), and these clients acted as the implicit reference group underlying the resulting ORs. Deviance tests comparing initial and final models were used to reassure that no important AP and C/V predictor had been omitted.

### 2.5.1 Kaplan-Meier survival curves

Kaplan-Meier survival curves were constructed for each antipsychotic drugs and carbamazepine and valproate. Log Rank tests were applied to the entire sample of conventional AP medication (chlorpromazine, haloperidol, pericyazine, thioridazine, trifluoperazine), atypical medication (amisulpride, olanzapine, quetiapine, risperidone), carbamazepine, valproate and mixed groups. The Log Rank test was then applied to sub-groups to assess if the result remained significant. The sub-groups analysed were: atypical AP drugs (amisulpride, olanzapine, quetiapine and risperidone), four conventional AP drugs (chlorpromazine, olanzapine, thioridazine and trifluoperazine) and carbamazepine and valproate.

### 2.5.2 Drug strength survival curves

Analysis of dose effects is difficult with dispensing data. Calculations for dose could not be made if there was only one dispensing. If there were only two dispensings, early filling of the second script would artificially inflate the calculated daily dose. The validity of average daily dose derived from dispensing data would improve as the number of dispensings increased. However ignoring those with few dispensings would introduce a bias against those whose death occurred after few dispensing. Secondly, 5-10% of RPBS dispensing are in non-standard quantities. We therefore used strength as a proxy for dose.

Survival curves were constructed for each AP drug by strength and formulation for incident and prevalent AP subjects. Oral solutions and preparations for injection (excluding long-acting depot preparations) were analysed as distinct groups. These preparations may not have been a proxy for dose but may have been proxies for other conditions, for example, aggression or physical frailty. Subjects whose prescriptions changed strength were classified separately in a mixed group.

In the incident AP subjects, the survival curves for different preparations of chlorpromazine, haloperidol, pericyazine and olanzapine were significant at the 5% level ($p<0.05$). However, for chlorpromazine and pericyazine the comparison groups were small and likely to distort the analysis. For olanzapine, the preparations of 7.5mg (N=8) and 10mg (N=11) had too few subjects for analysis. A reduced analysis was performed for preparation strengths of olanzapine 2.5mg (N=220) and olanzapine 5mg (N=157). The haloperidol groups were all sufficiently large. However, the injectable and oral solution group performed poorly. A reduced analysis of haloperidol was performed for the 0.5mg (N=858), 1.5mg (N=225) and 5mg (N=133) groups.

The prevalent AP subjects were analysed for dose effects in the same manner. Only variations in doses of olanzapine and haloperidol had significantly different survival curves. The olanzapine 2.5mg and 5mg preparations were analysed separately. For haloperidol the 0.5mg, 1.5mg and 5mg preparations were separately analysed.

### 2.5.3 Discontinuation survival curves

The survival of subjects who were discontinued from a study medication was followed from 60 days after the last dispensing of that medication. It was hypothesised that if drugs were contributing to an increase in the mortality rate, the cessation of the drugs, with an appropriate washout period, should be associated with the return of the mortality rate to a background rate reflecting age, gender and medical comorbidity.

### 2.5.4 Mortality Rates (death per 1000 person years of drug exposure)

The mortality rate for each drug was established for the four groups: incident AP or C/V subjects, prevalent AP or C/V subjects, incident AP or C/V subjects in Residential Aged Care Facilities at some point in 2003 or 2004 and incident AP or C/V users who had been prescribed a cholinesterase inhibitor between 2001 and 2004. For those who discontinued the drug, deaths occurring up to sixty days after the last dispensing were included in the drug associated mortality rate. Those who survived 60 days after discontinuing the drug, who started a second study drug or who were taking the drug and were alive at 31.12.04, were considered alive for the analysis.

### 2.5.5 Cox Regression (Survival Analysis)

Cox Regression models were developed for the incident and prevalent AP and C/V groups and the two sub-samples of the incident group. The relative risk of death was examined from date of first dispensing of a study drug to any of the following: death, sixty days after dispensing, the commencement of a second study drug or 31.12.04.

Haloperidol was the most frequently dispensed AP drug. However, haloperidol was associated with a much higher mortality rate and has been used in palliative care and in treating delirium [30]. A more meaningful comparison would be between atypical AP drugs or conventional AP drugs not used in palliative care. Thus, olanzapine, the second most commonly dispensed AP in the overall sample, was chosen as the reference drug.

Thus the relative risk for death was estimated for chlorpromazine, haloperidol, pericyazine, thioridazine, trifluoperazine, amisulpride, quetiapine, risperidone, carbamazepine, valproate and mixed group compared with olanzapine.

Covariates were age, sex, residential age care status (expressed as 2 dichotomous dummy variables: RACF-throughout-era versus Community-throughout-era and Mixed residential status-throughout-era versus community-throughout-era), antidepressants, benzodiazepines, lithium, anti-histamines, non-benzodiazepine anxiolytics, cholinesterase inhibitors, anti-arrhythmics, anti-hypertensives, anti-thrombotics, beta-blockers, calcium channel blockers, diuretics, glycosides, cholesterol lowering drugs, renin-angiotensin inhibitors, vasodilators, drugs used in diabetes, drugs used in Parkinson's disease (excluding anticholinergic drugs), drugs used in epilepsy (excluding carbamazepine, valproate and clonazepam), morphine, coxibs, drugs used in oncology and total number of different drugs in the year before first dispensing.

The unadjusted relative risk for death was estimated for chlorpromazine, haloperidol, pericyazine, thioridazine, trifluoperazine, amisulpride, quetiapine, risperidone, carbamazepine, valproate and mixed group. The covariates from the final model were applied to the drug results and adjusted results were developed. Finally drugs with p values >0.5 were omitted and final relative risk with 95% confidence intervals were established.

The relative risk of death was established for incident and prevalent AP and C/V groups and the incident sub-samples, over sixty days by repeating the above analysis but censoring the data 60 days after the first dispensing of a study drug, at death or when a second study drug was commenced.

Incident subjects whose primary cause of death or underlying cause of death was attributable to cancer in the AIHW data were removed from the sample. The relative risk of death was established for study drug groups using a Cox Regression model from date of dispensing until 31.12.04.

### 2.5.6 Case-control analysis

All subjects received a study date: either the date of death or a randomised date from 1.1.03. to 31.12.04. For those alive at 31.12.04, the random study dates were drawn from a distribution following the distribution of death dates. The pattern of AP and C/V dispensing was analysed for the 60 days prior to the study date. Logistic regression models were fitted with death status ("1"for dead and "0" for alive) as the endpoint or dependent variable. In this way AP and C/V exposure variables were defined for each client: they were exposed to their particular drug if and only if they had a prescription for it in the 60 days preceding their study date. Note that many clients were thus defined as not exposed, and these subjects form an implicit reference group against which the analysis contrasts death-odds among those exposed to their particular drug (i.e. there was no need to use a reference drug group such as olanzapine as was used in the Cox Regresssions).

### 2.5.7 Post-Hoc interactions

Age, gender and diuretic use were associated with an increased relative risk (RR) in the general incident cohort. These variables were considered as three binary covariates: old/young (divided at the median age), male/female and diuretic use/non-diuretic use. Thus for each drug eight distinct groups were established and the RR calculated using olanzapine, young, female, non-diuretic users as the reference group. Comparative relative risks were then established to explore within drug RR attributable to age, gender and diuretic use. For example, the RR associated with haloperidol, old, male, diuretic subjects was compared with the RR associated with haloperidol, old, male non-diuretic subjects to establish the RR associated with diuretic use in old, male haloperidol users. Thus for each drug there were four relevant comparisons for age, four for gender and four for diuretic use.

### 2.5.8 Cox Regression for end points other than death

Interactions were constructed for age, gender, diuretic dispensing and glycoside dispensing in a post hoc analysis. Date of admission for fractured femur and stroke in NSW and ACT public and private hospitals were extracted for the incident general cohort. General incident subjects with NSW or ACT postcodes were identified and formed the reduced cohort. Two Cox Regression models were constructed from date of dispensing of the study drug to the end points of admission for either fractured femur or stroke. As with the main analysis, subjects were censored on starting a second study drug, 60 days after discontinuation of the study drug or at 31.12.04. Unlike the main analysis where the end point was death, subjects who died in this analysis were censored. The model was adjusted for covariates and variables with partial p values >0.05 in the same manner as the main analysis.

# 3. RESULTS

## 3.1. INCIDENT ANTIPSYCHOTIC, CARBAMAZEPINE AND VALPROATE SUBJECTS

In 2003 and 2004 there were 16 634 incident antipsychotic, carbamazepine or valproate users among the DVA entitled beneficiaries 65 years and older. Fifty-six percent of subjects were male. Whilst only 14% resided in an Aged Care Facility on 1st January, 2003, 47% were resident in an Aged Care Facility at some point in 2003 or 2004. Twenty-four percent of the sample had died by 31.12.04. The age distribution of the subjects is given in Table 1.

*Table 1. Age distribution of incident antipsychotic, carbamazepine and valproate subjects at 1.1.03*

| Age in years at 2003 | N | Percent |
|---|---|---|
| 65-69 | 380 | 2% |
| 70-74 | 1009 | 6% |
| 75-79 | 4842 | 29% |
| 80-84 | 6291 | 38% |
| 85-89 | 3127 | 19% |
| 90-94 | 853 | 5% |
| 95-99 | 110 | 1% |
| 100+ | 22 | 0% |

There were sufficient subjects to analyse data for five conventional antipsychotic drugs, four atypical antipsychotic drugs, and two anti-epileptic drugs, carbamazepine and valproate. Two subjects dispensed aripiprazole were omitted from the analysis. Those who were incident users for any two of our study drugs simultaneously were entered into the mixed group. Incident users who started a second study drug were included in the first drug group and censored as alive at the point of starting the second drug. The average age, percentage male and residential status of subjects in each drug group are displayed in Table 2.

*Table 2. Incident antipsychotic, carbamazepine and valproate subjects by age, sex and place of residence in 2003 and 2004*

| | N | Mean Age | Percentage Male | Community | RACF[1] | Mixed[2] |
|---|---|---|---|---|---|---|
| Conventional AP drug | | | | | | |
| Chlorpromazine | 511 | 81.1 | 67% | 73% | 26% | 1% |
| Haloperidol | 4739 | 82.67 | 60% | 52% | 41% | 7% |
| Pericyazine | 972 | 83.05 | 57% | 44% | 50% | 6% |
| Thioridazine | 56 | 80.13 | 52% | 79% | 20% | 2% |
| Trifluoperazine | 243 | 80.19 | 41% | 82% | 15% | 3% |
| Atypical AP drugs | | | | | | |
| Amisulpride | 48 | 81.56 | 54% | 65% | 29% | 6% |
| Olanzapine | 2387 | 82.21 | 50% | 44% | 47% | 9% |
| Quetiapine | 394 | 81.15 | 60% | 52% | 38% | 10% |
| Risperidone | 1451 | 82.54 | 53% | 39% | 52% | 8% |
| Others | | | | | | |
| Carbamazepine | 2819 | 80.24 | 55% | 88% | 11% | 1% |
| Valproate | 2857 | 80.41 | 55% | 76% | 19% | 5% |
| Mixed | 155 | 81.78 | 62% | 34% | 57% | 10% |

[1]Residential Aged Care Facility

[2]Some dispensing occurred in the community and some in RACF

All descriptive characteristics, psychotropic medication dispensing and dispensing of other medication were significantly different across the study drug groups given the large sample ($p<0.001$). All variables presented (except anticholinergic drug dispensing) were used as covariates in the Cox regression and logistic regression models. Carbamazepine (88%), trifluoperazine (82%), thioridazine (79%), valproate (76%) and chlorpromazine (73%) had the highest percentage of subjects receiving all dispensings in the community. Entry (or exit) from a residential aged care facility occurred in 10% of quetiapine and mixed subjects, 9% of olanzapine subjects, 8% of risperidone subjects, and 7% of haloperidol subjects.

The pattern of psychotropic medication dispensing in 2003 and 2004 is contained in Table 3. Antihistamines were available without a prescription. The data only captured antihistamines dispensed with a prescription, hence the results may underestimate the true use of these drugs. The use of cholinesterase inhibitors varied across drug groups.

*Table 3. Incident antipsychotic, carbamazepine and valproate subjects by dispensing of other classes of psychotropic medications in 2003 and 2004*

| | Antidepressant use | Lithium use | BZDP use | Cholinesterase Inhibitor use | Antihistamine use |
|---|---|---|---|---|---|
| Conventional AP drug | | | | | |
| Chlorpromazine | 47% | 1% | 62% | 8% | 21% |
| Haloperidol | 47% | 1% | 64% | 15% | 13% |
| Pericyazine | 53% | 1% | 63% | 21% | 10% |
| Thioridazine | 55% | 0% | 64% | 5% | 16% |
| Trifluoperazine | 54% | 0% | 60% | 7% | 16% |
| Atypical AP drugs | | | | | |
| Amisulpride | 63% | 2% | 58% | 4% | 8% |
| Olanzapine | 56% | 2% | 62% | 20% | 11% |
| Quetiapine | 55% | 2% | 61% | 30% | 9% |
| Risperidone | 53% | 2% | 57% | 24% | 11% |
| Others | | | | | |
| Carbamazepine | 45% | 0% | 53% | 3% | 21% |
| Valproate | 49% | 1% | 54% | 6% | 17% |
| Mixed | 56% | 4% | 74% | 21% | 9% |

The selected pattern of medical drug dispensing for the subjects is displayed in Table 4. Unsurprisingly, the use of other anti-epileptic drugs was higher in the carbamazepine and valproate subjects. Morphine dispensing varied among the groups, with 28% of the haloperidol subjects receiving morphine. Oncological drug use also varied significantly.

*Table 4. Incident antipsychotic, carbamazepine and valproate subjects by dispensing of selected classes of medications in 2003 and 2004*

| | Diuretic use | Glycoside use | Anti-epileptic drug use[1] | Morphine use | Coxib use | Oncological drug use |
|---|---|---|---|---|---|---|
| Conventional AP drugs | | | | | | |
| Chlorpromazine | 40% | 15% | 6% | 16% | 28% | 11% |
| Haloperidol | 45% | 18% | 5% | 28% | 27% | 8% |
| Pericyazine | 41% | 15% | 3% | 15% | 26% | 5% |
| Thioridazine | 43% | 20% | 7% | 5% | 34% | 5% |
| Trifluoperazine | 40% | 12% | 3% | 7% | 33% | 5% |
| Atypical AP drugs | | | | | | |
| Amisulpride | 25% | 8% | 4% | 8% | 17% | 4% |
| Olanzapine | 38% | 14% | 4% | 12% | 26% | 4% |
| Quetiapine | 34% | 14% | 3% | 5% | 32% | 5% |
| Risperidone | 39% | 15% | 4% | 12% | 24% | 4% |
| Others | | | | | | |
| Carbamazepine | 45% | 15% | 16% | 12% | 36% | 8% |
| Valproate | 43% | 13% | 16% | 13% | 35% | 8% |
| Mixed | 37% | 16% | 7% | 16% | 30% | 5% |

[1]Anti-epileptic drugs excluding carbamazepine, valproate and clonazepam

The use of drugs for some movement disorders is detailed in Table 5. Quetiapine and to some extent, olanzapine, were more frequently dispensed to those who presumably had Parkinson's disease. It was hypothesised that anticholinergic drugs dispensed in the absence of drugs for Parkinson's disease would be a marker for extra-pyramidal side effects from antipsychotic medication. Trifluoperazine and amisulpride were associated with increased dispensing of anticholinergic medication in the absence of other drugs used in Parkinson's disease.

*Table 5. Incident antipsychotic, carbamazepine and valproate subjects by dispensing of drugs used in movement disorders in 2003 and 2004*

| | Drugs for Parkinson's disease[1] | Anti-cholinergic drugs | Anti-cholinergic drugs without other drugs for Parkinson's Disease |
|---|---|---|---|
| Conventional AP drugs | | | |
| Chlorpromazine | 5% | 1% | 1% |
| Haloperidol | 5% | 2% | 1% |
| Pericyazine | 6% | 1% | 1% |
| Thioridazine | 7% | 0% | 0% |
| Trifluoperazine | 5% | 5% | 5% |
| Atypical AP drugs | | | |
| Amisulpride | 8% | 6% | 6% |
| Olanzapine | 10% | 2% | 1% |
| Quetiapine | 29% | 4% | 1% |
| Risperidone | 7% | 2% | 1% |
| Others | | | |
| Carbamazepine | 4% | 1% | 0% |
| Valproate | 6% | 1% | 1% |
| Mixed | 6% | 2% | 2% |

[1]Excluding anti-cholinergic drugs

The total number of different drugs in a 12 month period performed well as a predictor of mortality[27]. The total number of distinct drugs over 12 months were calculated at three monthly intervals. The total score, prior to the index dispensing of antipsychotic, carbamazepine and valproate medication, was extracted for the each subject and the mean for each drug established. The results are displayed in Table 6. Chlorpromazine (13.56),

carbamazepine (13.71), valproate (12.98) and haloperidol (12.29) subjects had the highest mean scores.

*Table 6. Incident antipsychotic, carbamazepine and valproate subjects by mean of different drug count in the year preceding first dispensing in 2003 or 2004*

| | N | Average of total number of different drugs over 12 months |
|---|---|---|
| Conventional AP drug | | |
| Chlorpromazine | 511 | 13.56 |
| Haloperidol | 4739 | 12.29 |
| Pericyazine | 972 | 10.00 |
| Thioridazine | 56 | 11.16 |
| Trifluoperazine | 243 | 10.58 |
| Atypical AP drugs | | |
| Amisulpride | 48 | 10.54 |
| Olanzapine | 2387 | 10.63 |
| Quetiapine | 394 | 11.19 |
| Risperidone | 1451 | 10.62 |
| Others | | |
| Carbamazepine | 2819 | 13.71 |
| Valproate | 2857 | 12.98 |
| Mixed | 155 | 10.29 |

Death per 1000 person years at risk (pyar) is displayed in Table 7. Chlorpromazine and haloperidol were associated with significantly increased mortality rates, 483 and 909 deaths per 1000 pyar respectively ($p<0.005$ compared with the mortality rates for all other study drugs). Thioridazine, trifluoperazine and carbamazepine were associated with relatively low death rates, 76, 96 and 102 deaths per 1000 pyar respectively. The small size of the amisulpride group is reflected in the large 95% confidence interval (CI). There was strong evidence that the mortality rates for risperidone and quetiapine were significantly different ($p<0.05$).

*Table 7. Incident antipsychotic, carbamazepine and valproate subjects by deaths per 1000 person years of exposure in 2003 or 2004*

| | N | Alive[1] | Dead[2] | Deaths per 1000 person years at risk | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| Conventional AP drugs | | | | | | |
| Chlorpromazine | 511 | 83% | 17% | 483 | 386 | 597 |
| Haloperidol | 4739 | 68% | 32% | 909 | 864 | 957 |
| Pericyazine | 972 | 89% | 11% | 219 | 180 | 265 |
| Thioridazine | 56 | 95% | 5% | 76 | 15 | 222 |
| Trifluoperazine | 243 | 95% | 5% | 96 | 50 | 168 |
| Atypical AP drugs | | | | | | |
| Amisulpride | 48 | 85% | 15% | 346 | 139 | 713 |
| Olanzapine | 2387 | 84% | 16% | 246 | 222 | 272 |
| Quetiapine | 394 | 90% | 10% | 172 | 124 | 234 |
| Risperidone | 1451 | 86% | 14% | 276 | 240 | 317 |
| Others | | | | | | |
| Carbamazepine | 2819 | 96% | 4% | 102 | 85 | 122 |
| Valproate | 2857 | 91% | 9% | 190 | 168 | 214 |
| Mixed | 155 | 76% | 24% | 355 | 250 | 489 |

[1]Subjects were considered alive if they were alive when starting a second study drug, were alive 60 days after discontinuation of a study drug or alive on 31.12.04.

[2]Death was considered to have occurred during the drug exposure if the death occurred 60 days after the last drug dispensing.

### 3.1.1 Kaplan-Meier Survival Curves and Log Rank Tests

Kaplan-Meier survival curves were plotted for incident antipsychotic, carbamazepine and valproate subjects. As stated in the methodology section, subjects who commenced a second study drug were censored as alive at the point of commencing the second drug. Subjects who discontinued the medication were followed for 60 days after the last dispensing and then censored.

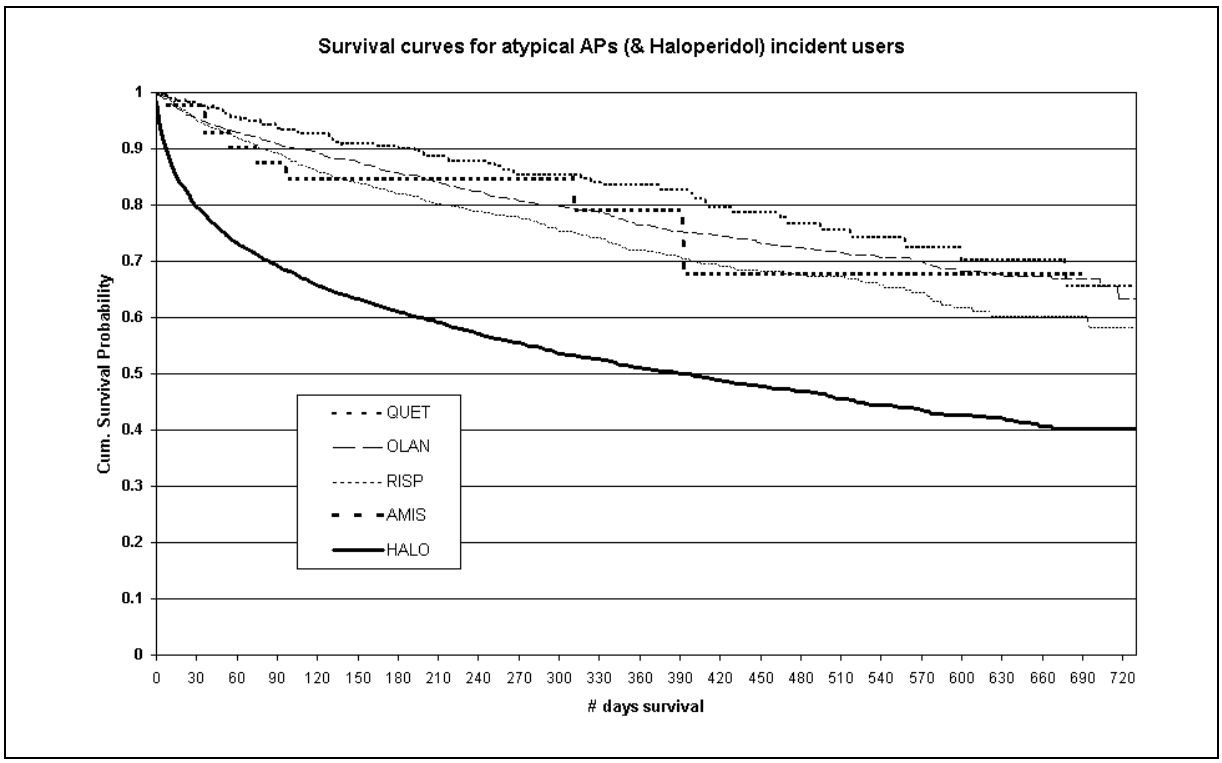



*Figure 1. Survival curves for atypical antipsychotic drugs (with haloperidol added for comparison) in incident antipsychotic subjects.*

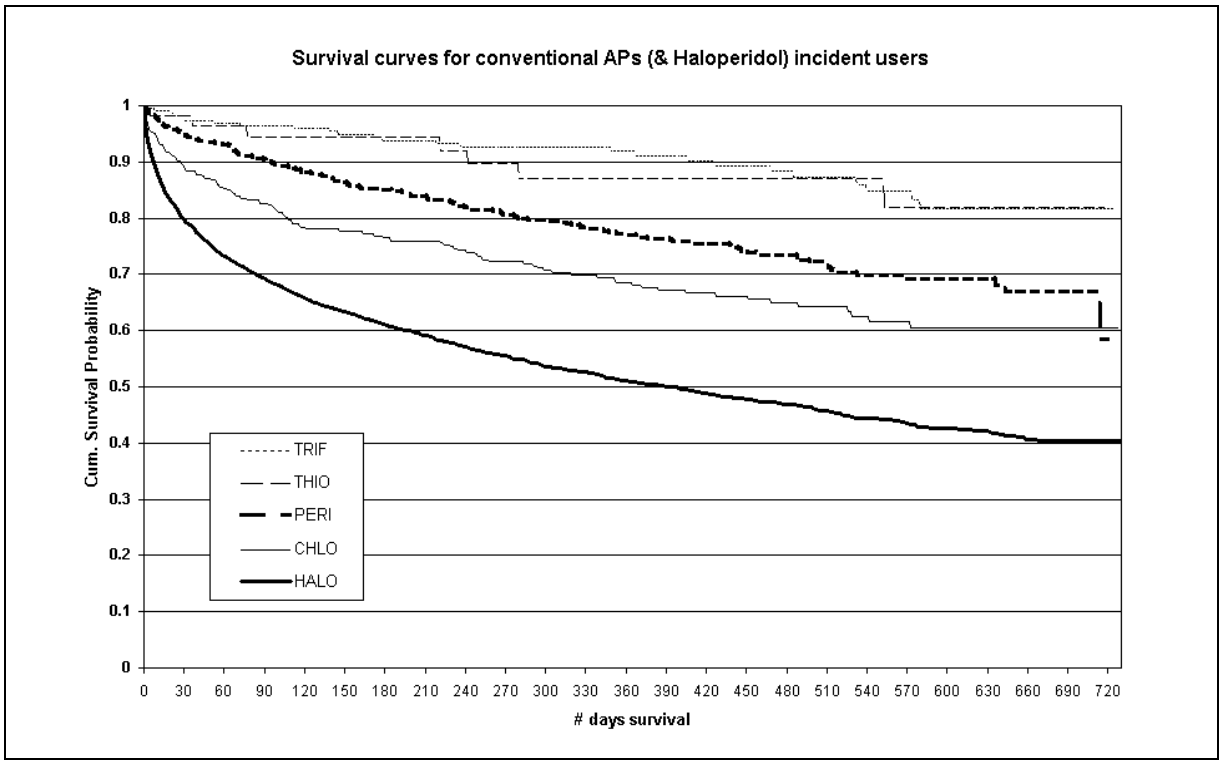


*Figure 2. Survival curves for conventional antipsychotic drugs in incident antipsychotic subjects.*

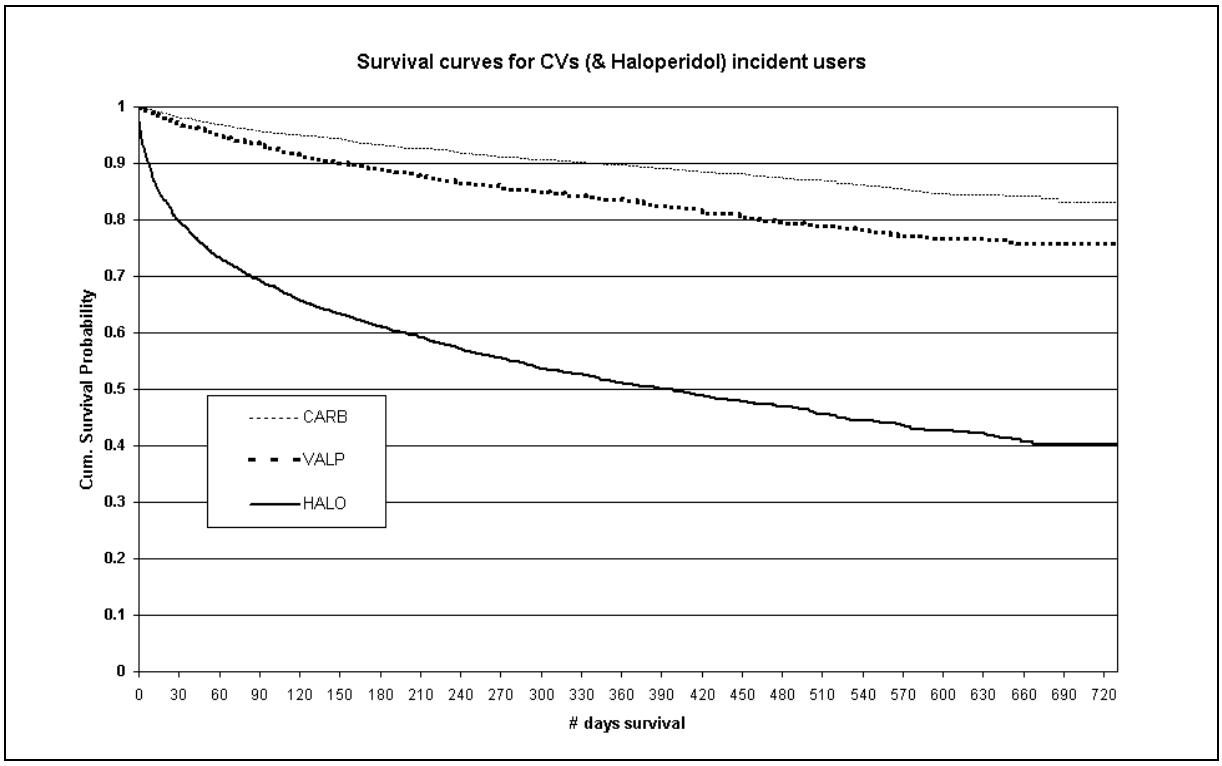



*Figure 3. Survival curves for carbamazepine and valproate (with haloperidol added for comparison) in incident haloperidol, carbamazepine or valproate subjects.*

Haloperidol was associated with reduced survival. The first 60 days was associated with marked reduction in survival. The Log Rank test for all twelve drugs (including the mixed group), with 11 degrees of freedom, was highly significant ($p<0.001$). Haloperidol was then removed from the analysis and drugs analysed in groups to ascertain if differences in survival for the remaining drug groups were significant. The results are presented in Table 8.

*Table 8. Group Log Rank tests for survival curves in incident antipsychotic, carbamazepine or valproate subjects*

| Model | Statistic | df | p-value |
|---|---|---|---|
| All 12 drugs (AP,C,V, mixed) | 1901.85 | 11 | <0.001 |
| Atypical AP (4) | 14.92 | 3 | 0.002 |
| Conventional AP, excluding haloperidol (4) | 44.78 | 3 | <0.001 |
| Carbamazepine or Valproate | 43.06 | 1 | <0.001 |

Thus, among the atypical antipsychotic drugs—amisulpride, olanzapine, quetiapine and risperidone—the survival curves were significantly different ($p=0.002$). From the graph, quetiapine was associated with better survival rates and risperidone with the poorer survival rates. The conventional antipsychotic medications—chlorpromazine, pericyazine, thioridazine and trifluoperazine—had differences in survival rates that were highly significant ($p <0.001$). Chlorpromazine was associated with poorer survival rates and thioridazine and trifluoperazine with better outcomes. Carbamazepine and valproate differed significantly in the associated survival times ($p<0.001$), with valproate associated with poorer

outcomes. Haloperidol was included in the survival graphs to provide a comparison curve but was excluded from the sub-group Log Rank tests, as it was associated with significantly poorer outcomes compared with all other study drugs.

### 3.1.2 Kaplan-Meier survival curves for differing antipsychotic formulations

Individual antipsychotic drugs were considered by their formulation, that is by different strengths, oral solution and short-acting parenteral forms. As stated previously, depot medications were excluded. Dosage, or its proxy strength, could not be measured for the oral solution or short-acting parenteral forms. These preparations may be associated with aggression, resistance to care or difficulty swallowing. Table 9 displays the percentage of subjects in each antipsychotic drug group receiving only the lowest strength tablet or wafer throughout 2003 and 2004.

*Table 9. Incident antipsychotic, carbamazepine and valproate subjects by percentage of subjects receiveing only the lowest strength tablet or wafer preparation in 2003 and 2004.*

| | N | Percentage only receiving lowest strength tablet or wafer preparation |
|---|---|---|
| Conventional AP drug | | |
| Chlorpromazine | 511 | 40% |
| Haloperidol | 4739 | 58% |
| Pericyazine | 972 | 93% |
| Thioridazine | 56 | 43% |
| Trifluoperazine | 243 | 66% |
| Atypical AP drugs | | |
| Amisulpride | 48 | 52% |
| Olanzapine | 2387 | 42% |
| Quetiapine | 394 | 79% |
| Risperidone | 1451 | 85% |

Survival curves were established for each antipsychotic drug by formulation. The various survival curves pertaining to each antipsychotic drug were compared using the Log Rank test. The curves for chlorpromazine, haloperidol, pericyazine and olanzapine incident subjects were significant. One of the two pericyazine curves had small numbers which would have distorted the Log Rank test (pericyazine 10mg, N=9). The chlorpromazine parenteral preparation (N=7) and oral solution (N=18) had much poorer outcomes than other chlorpromazine preparations but the numbers in these groups were small. Two olanzapine groups had small numbers which would have distorted the Log Rank test (olanzapine 7.5mg, N=8 and olanzapine 10mg, N= 11). The survival curves for olanzapine 2.5mg (N=220) and olanzapine 5mg (N=157) were compared and not found to be significantly different (p=0.97).

Haloperidol associated survival curves were constructed for the following preparations: 0.5mg, 1.5mg, 5mg, oral and parenteral formulations, and mixed dosage. The mixed group represented those who had at least one change in haloperidol preparation. The survival curves are represented in Figure 4. The individual haloperidol preparations had large numbers in each group. As can be seen from the graph, parenteral preparations and oral solutions, which were coded “99”, were associated with poorer outcomes.

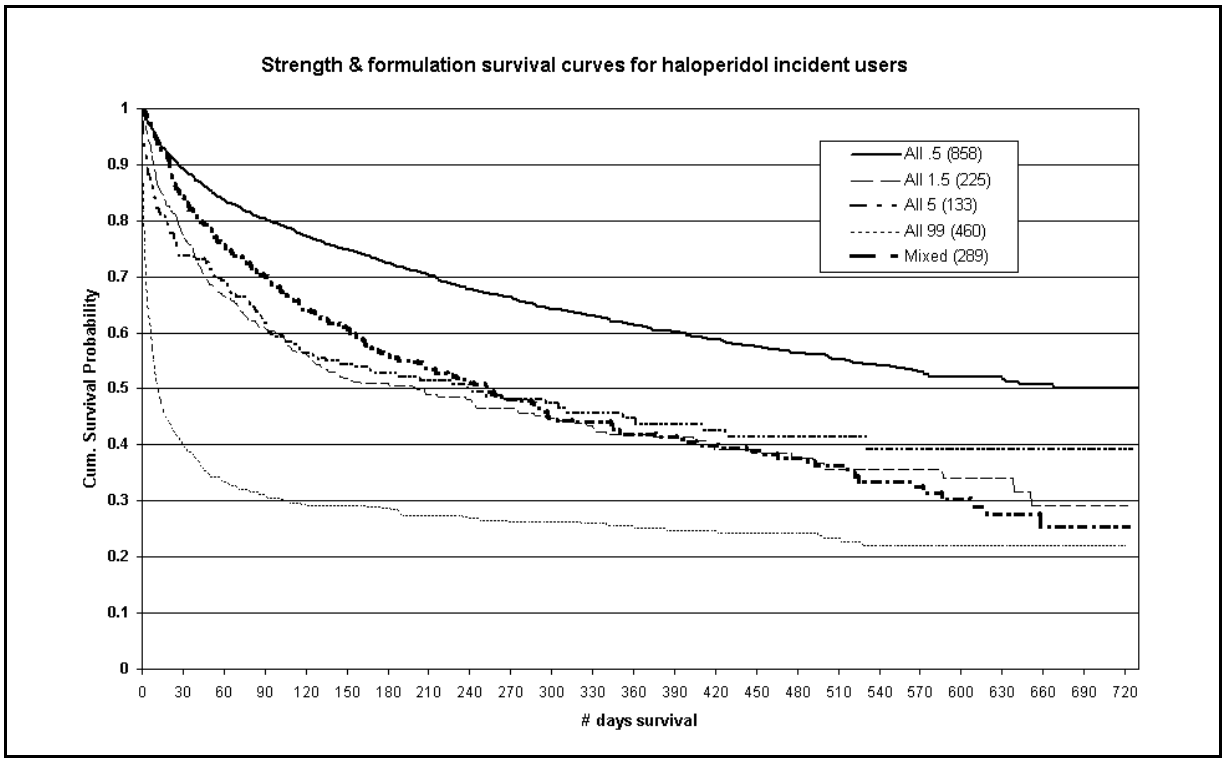



*Figure 4. Survival Curves for incident Haloperidol subjects by Strength and Formulation*

To establish if there were any significant differences in survival associated with haloperidol 0.5mg, 1.5mg and 5mg preparations, these survival curves were compared using the Log Rank test. Among the three haloperidol strengths, there was very strong evidence that haloperidol 0.5mg was associated with better survival outcomes compared with haloperidol 1.5mg and haloperidol 5mg in incident subjects ($p<0.001$).

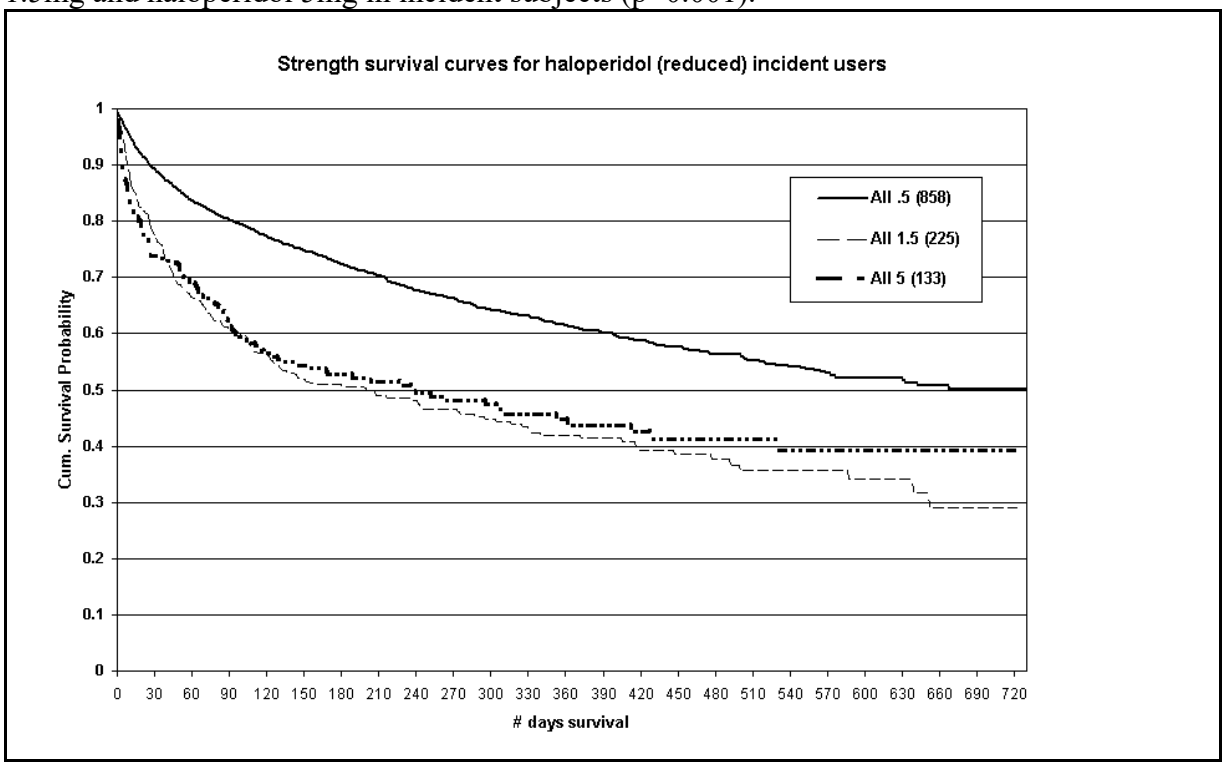


*Figure 5. Strength survival curves for incident Haloperidol subjects*

### 3.1.3 Survival curves for incident subjects discontinuing antipsychotic medication

If any of the study drugs were truly toxic, it was hypothesised that after a suitable wash out period, discontinuation of the drug should result in an improvement in survival rates. Survival should then reflect the age gender and medical comorbidities of the subjects. The survival curve for those discontinuing haloperidol improved compared with those continuing on the medication. Only 17 subjects discontinued amisulpride and 36 subjects discontinued thioridazine. These groups were not included in the survival graphs. The survival curve of those who discontinued haloperidol approached the curves of those who discontinued atypical antipsychotic medication. However, the survival associated with discontinuation in the trifluoperazine, carbamazepine and valproate subjects were superior to the curve associated with haloperidol discontinuation, suggesting that subjects in the former groups may differ on important characteristics from the haloperidol group.

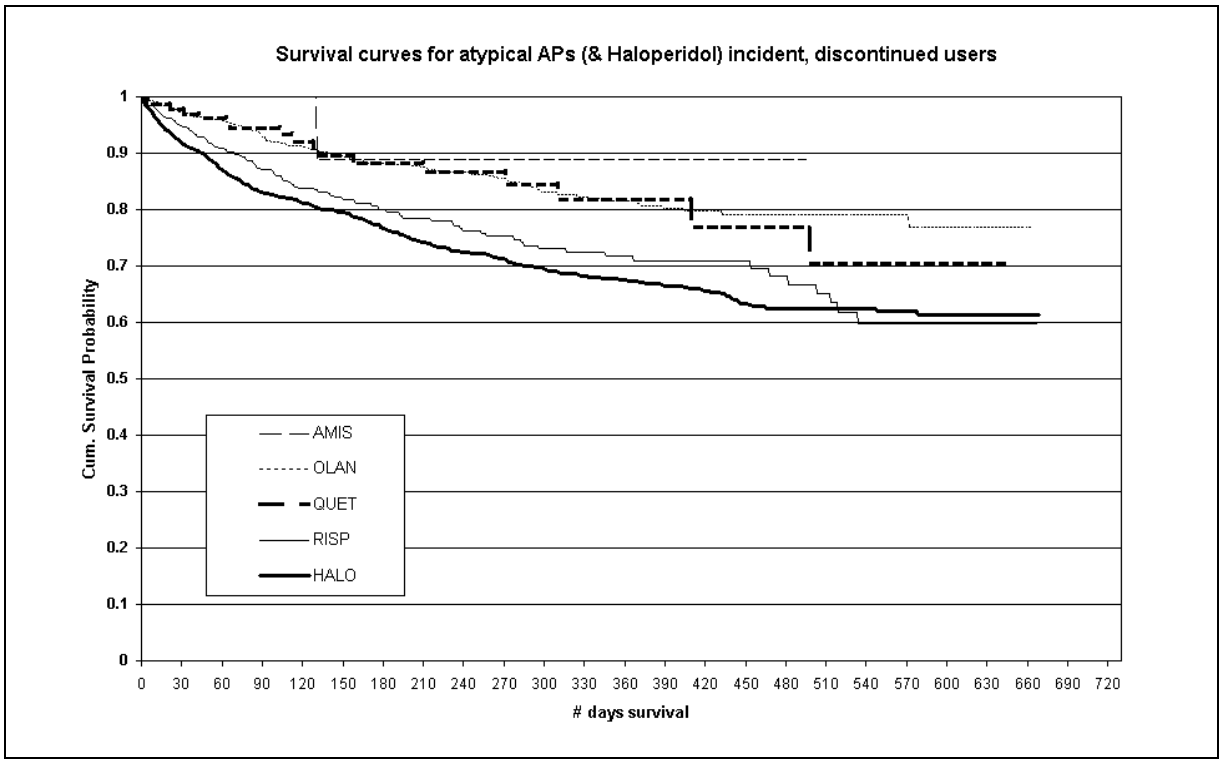



*Figure 6. Survival Curves for incident atypical antipsychotic subjects who discontinued antipsychotic medication (haloperidol included for comparison)*

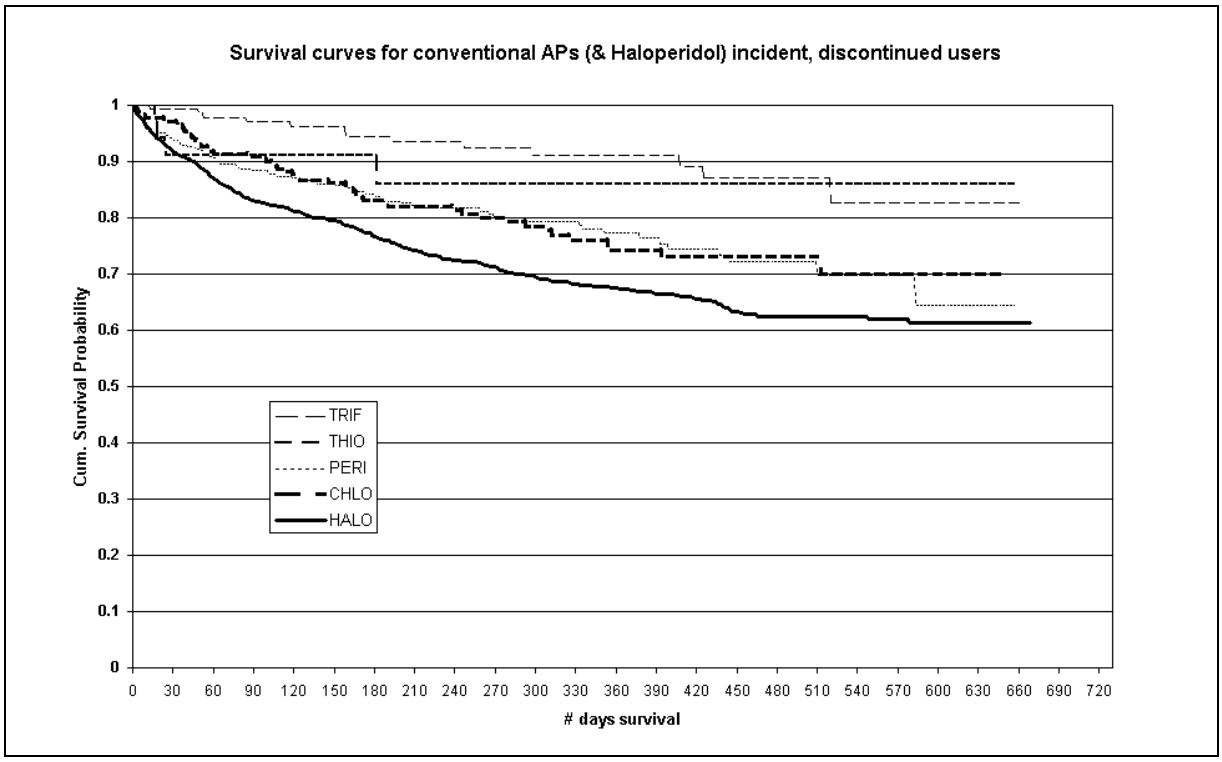



*Figure 7. Survival Curves for incident conventional antipsychotic subjects who discontinued antipsychotic medication*

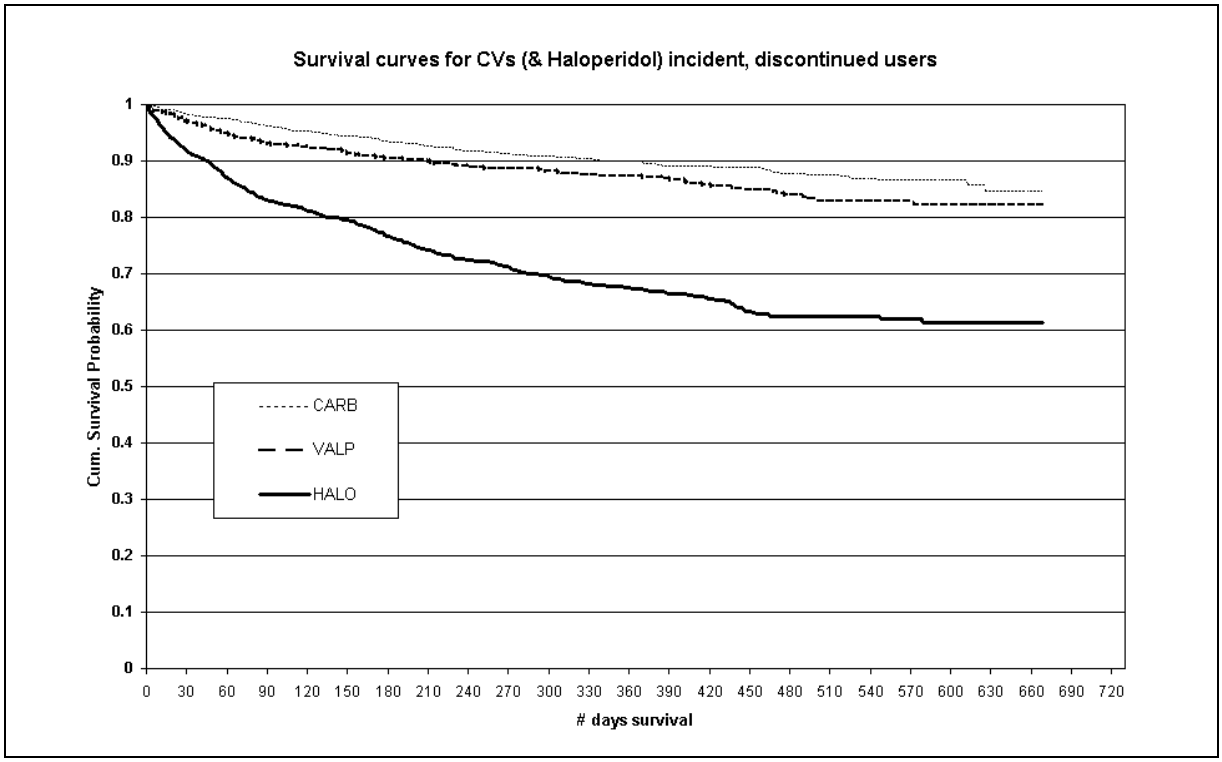



*Figure 8 Survival Curves for incident carbamazepine and valproate subjects who discontinued antipsychotic medication (haloperidol included for comparison)*

## 3.1.4 Survival Analysis for incident subjects

### 3.1.4.1 Survival Analysis to 31.12.04

The Relative Risk (RR) of death until 31.12.04. was established using a multivariate Cox Regression. The results from the final model are displayed in Table 10. Variables with a partial p value greater or equal than 0.05 have been omitted. Olanzapine was chosen as the reference group, hence the relative risks presented are with respect to the olanzapine group.

*Table 10. Relative risk of death from initial dispensing to 31.12.04 in incident antipsychotic, carbamazepine and valproate subjects*[1]

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Chlorpromazine | 1.39 | <0.001 | 1.15 | 1.67 |
| Haloperidol | 2.26 | <0.001 | 2.08 | 2.47 |
| Risperidone | 1.23 | 0.003 | 1.07 | 1.40 |
| Trifluoperazine | 0.55 | 0.003 | 0.37 | 0.82 |
| Carbamazepine | 0.43 | <0.001 | 0.37 | 0.50 |
| Valproate | 0.71 | <0.001 | 0.63 | 0.80 |
| Multiple study drugs | 1.48 | 0.009 | 1.10 | 1.98 |
| Sex (Males high) | 1.55 | <0.001 | 1.45 | 1.66 |
| Age | 1.02 | <0.001 | 1.01 | 1.03 |
| RACF[2] (high) vs Community | 1.11 | <0.006 | 1.03 | 1.19 |
| Mixed[3] (high) vs Community | 0.60 | <0.001 | 0.52 | 0.70 |
| Antidepressants | 0.71 | <0.001 | 0.67 | 0.76 |
| Cholinesterase Inhibitors | 0.62 | <0.001 | 0.56 | 0.69 |
| Lithium | 0.53 | 0.009 | 0.33 | 0.85 |
| Antihistamines | 0.67 | <0.001 | 0.60 | 0.74 |
| Antithrombotics | 0.82 | <0.001 | 0.76 | 0.87 |
| Beta blockers | 0.90 | 0.008 | 0.83 | 0.97 |
| Calcium channel blockers | 0.87 | <0.001 | 0.80 | 0.94 |
| Diuretics | 1.23 | <0.001 | 1.15 | 1.32 |
| Glycosides | 1.10 | 0.032 | 1.01 | 1.19 |
| Lipid reducers | 0.78 | <0.001 | 0.72 | 0.85 |
| Renin-angiotensives | 0.89 | 0.001 | 0.83 | 0.96 |
| Morphine use | 3.63 | <0.001 | 3.39 | 3.89 |
| Coxib use | 0.69 | <0.001 | 0.64 | 0.75 |
| Cancer drug use | 1.31 | <0.001 | 1.17 | 1.46 |
| Total number of different drugs[4] | 1.03 | <0.001 | 1.02 | 1.03 |

[1]Olanzapine subjects as the reference group
[2]Residential Aged Care Facility
[3]Dispensing partly in the community and partly in RACF
[4]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

The RR for chlorpromazine 1.39 (p value <0.001, 95%CI, 1.15-1.67), haloperidol 2.26 (p value <0.001, 95% CI, 2.08-2.47), risperidone 1.23 (p value 0.003, 95% CI, 1.07-1.40) and multiple study drug group 1.48 (p value 0.009, 95% CI, 1.10-1.98) were significant when compared with olanzapine subjects. Trifluoperazine, carbamazepine and valproate were associated with a significant reduction in RR. Male sex, increasing age and residence in an aged care facility during the period of dispensing were associated with increased RR. Diuretic, glycoside, morphine and cancer drug use was associated with an increased RR. Morphine use was a particularly strong predictor of death. The total number of different drugs in the year prior to the index dispensing was also associated with an increase in RR. A number of drugs were associated with a lower RR. Coxibs which have been associated with adverse coronary events at certain doses[112], were associated with a reduced RR.

### 3.1.4.2 Survival Analysis over 60 days

A multivariate Cox regression ascertained the RR at 60 days for each study drug. The resulted are presented in Table 11. Again variables with a partial p value greater or equal to 0.05 have been omitted. Olanzapine was the reference group.

*Table 11. Relative risk of death over 60 days with the olanzapine subjects as the reference group in incident antipsychotic, carbamazepine and valproate subjects*[1]

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Chlorpromazine | 1.31 | 0.004 | 1.09 | 1.57 |
| Haloperidol | 2.22 | <0.001 | 2.04 | 2.42 |
| Risperidone | 1.23 | 0.003 | 1.07 | 1.40 |
| Trifluoperazine | 0.49 | 0.001 | 0.33 | 0.73 |
| Carbamazepine | 0.38 | <0.001 | 0.33 | 0.44 |
| Valproate | 0.65 | <0.001 | 0.57 | 0.73 |
| Multiple study drugs | 1.46 | 0.011 | 1.09 | 1.96 |
| Sex (Males high) | 1.52 | <0.001 | 1.42 | 1.63 |
| Mixed[2] (high) vs Community | 0.57 | <0.001 | 0.49 | 0.66 |
| Antidepressants | 0.70 | <0.001 | 0.66 | 0.75 |
| Anti-Parkinson's | 0.86 | 0.024 | 0.76 | 0.98 |
| Cholinesterase Inhibitors | 0.63 | <0.001 | 0.56 | 0.70 |
| Lithium | 0.52 | <0.007 | 0.32 | 0.84 |
| Antithrombotics | 0.81 | <0.001 | 0.76 | 0.87 |
| Calcium channel blockers | 0.84 | <0.001 | 0.77 | 0.90 |
| Diuretics | 1.23 | <0.001 | 1.15 | 1.32 |
| Lipid reducers | 0.71 | <0.001 | 0.66 | 0.77 |
| Morphine use | 3.81 | <0.001 | 3.56 | 4.08 |
| Coxib use | 0.67 | <0.001 | 0.62 | 0.72 |
| Total number of different drugs[3] | 1.03 | <0.001 | 1.02 | 1.03 |

[1]Olanzapine subjects as the reference group

[2] Dispensing partly in the community and partly in RACF

[3]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

The results of the survival analysis for the study drugs over 60 days are consistent with the analysis over the longer period. Age and residence in an Aged Care Facility over the entire period of dispensing were no longer significant predictors in this model. Similarly, glycoside and cancer drug use were no longer significant predictors.

### 3.1.4.3 Survival Analysis over 730 days with the National Death Index cancer deaths removed

Table 11 compares the survival analysis from Table 10 with the analysis adjusted to remove cancer deaths identified by the Australian Institute of Health and Welfare's data. Only variables with a partial p value of 0.05 were presented. Australian Institute of Health and Welfare's National Death Index provided a perfect match for only 53% of deaths in the combined incident and prevalent antipsychotic, carbamazepine and valproate users (4485/8417). Whilst excluding the cancer deaths reduced the RR of death associated with chlorpromazine and haloperidol, the resulting RR for these drugs remained significant. There was no change in the RR associated with risperidone. There were minor changes to the RR associated with anti-arrhythmic, antithrombotic and angiotensin converting enzyme inhibitors and receptor blocking drugs. The predictive strength of oncological drug use was reduced when cancer deaths were excluded.

*Table 12. Survival Analysis from Table 9 compared with Survival analysis until 31.12.04. with National Death Index cancer deaths removed*[1]

| Analysis | Cox regressions (RRs) | | |
|---|---|---|---|
| Survival time | To 31-Dec-04 | To 31-Dec-04 | To 31-Dec-04 |
| Population | Incident | Incident (without AIHW Cancer deaths) | P values for reduced Cox regression |
| n | 16632 | 15820 | 15820 |
| Chlorpromazine | 1.39 | 1.32 | 0.011 |
| Haloperidol | 2.26 | 2.01 | <0.001 |
| Risperidone | 1.23 | 1.23 | 0.003 |
| Trifluoperazine | 0.55 | 0.60 | 0.018 |
| Carbamazepine | 0.43 | 0.43 | <0.001 |
| Valproate | 0.71 | 0.70 | <0.001 |
| Multiple study drugs | 1.48 | 1.42 | 0.027 |
| Sex (Males high) | 1.55 | 1.54 | <0.001 |
| Age | 1.02 | 1.03 | <0.001 |
| RACF[2] (high) vs Community | 1.11 | 1.37 | <0.001 |
| Mixed[3] (high) vs Community | 0.60 | 0.71 | <0.001 |
| Antidepressants | 0.71 | 0.73 | <0.001 |
| Cholinesterase inhibitor | 0.62 | 0.69 | <0.001 |
| Lithium | 0.53 | 0.59 | 0.041 |
| Antiarrhythmics | | 1.18 | 0.023 |
| Antihistamines | 0.67 | 0.70 | <0.001 |
| Antithrombotics | 0.82 | | |
| Beta blockers | 0.90 | 0.89 | 0.007 |
| Calcium channel blockers | 0.87 | 0.88 | 0.004 |
| Diuretics | 1.23 | 1.26 | <0.001 |
| Glycosides | 1.10 | 1.12 | 0.018 |
| Lipid reducers | 0.78 | 0.75 | <0.001 |
| Renin-angiotensives | 0.89 | | |
| Morphine drug use | 3.63 | 3.35 | <0.001 |
| Coxib use | 0.69 | 0.71 | <0.001 |
| Cancer drug use | 1.31 | 1.18 | 0.016 |
| Total number of different drugs[4] | 1.03 | 1.02 | <0.001 |

[1]Olanzapine subjects as the reference group

[2]Residential Aged Care Facility

[3] Dispensing partly in the community and partly in RACF

[4]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

## 3.1.5 Odds Ratios (ORs) of death in the Case Control Analysis

The results from the logistic regression comparing exposure to drugs over a sixty day study period are displayed in Table 13. The sixty day study period was either the sixty days prior to death or sixty days prior to a randomised study date. Olanzapine was not used as a reference group in this analysis. The reference group was formed by those not taking any study drug in the study period. Amisulpride was excluded from the analysis as there were too few subjects.

*Table 13. Odds Ratios of death from the case control study of drug exposure 60 days prior to date of death or a randomised study date in incident antipsychotic, carbamazepine or valproate users*[1]

| Predictor | OR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Chlorpromazine | 9.74 | <0.001 | 6.70 | 14.18 |
| Haloperidol | 19.24 | <0.001 | 16.91 | 21.89 |
| Olanzapine | 4.75 | <0.001 | 4.06 | 5.55 |
| Pericyazine | 3.67 | <0.001 | 2.80 | 4.81 |
| Quetiapine | 4.28 | <0.001 | 2.90 | 6.32 |
| Risperidone | 6.29 | <0.001 | 5.09 | 7.77 |
| Trifluoperazine | 2.95 | 0.002 | 1.51 | 5.76 |
| Carbamazepine | 2.38 | <0.001 | 1.89 | 3.00 |
| Valproate | 4.59 | <0.001 | 3.85 | 5.47 |
| Multiple study drugs | 10.17 | <0.001 | 6.06 | 17.05 |
| Sex (Males high) | 1.67 | <0.001 | 1.52 | 1.83 |
| Age | 1.05 | <0.001 | 1.04 | 1.06 |
| RACF[2] (high) vs Community | 1.25 | <0.001 | 1.13 | 1.38 |
| Mixed[3] (high) vs Community | 0.56 | <0.001 | 0.46 | 0.69 |
| Antidepressants | 0.71 | <0.001 | 0.65 | 0.78 |
| Anti-epilepsy | 0.80 | 0.010 | 0.67 | 0.95 |
| Cholinesterase Inhibitors | 0.63 | <0.001 | 0.55 | 0.73 |
| Lithium | 0.49 | 0.013 | 0.28 | 0.86 |
| Antiarrhythmics | 1.44 | <0.001 | 1.19 | 1.73 |
| Antihistamines | 0.60 | <0.001 | 0.52 | 0.69 |
| Antihypertensives | 0.79 | 0.026 | 0.64 | 0.97 |
| Antithrombotics | 0.82 | <0.001 | 0.75 | 0.91 |
| Beta blockers | 0.87 | 0.012 | 0.78 | 0.97 |
| Calcium channel blockers | 0.85 | 0.004 | 0.76 | 0.95 |
| Diuretics | 1.24 | <0.001 | 1.12 | 1.36 |
| Glycosides | 1.28 | <0.001 | 1.13 | 1.44 |
| Lipid reducers | 0.73 | <0.001 | 0.65 | 0.82 |
| Morphine use | 4.63 | <0.001 | 4.15 | 5.17 |
| Coxib use | 0.63 | <0.001 | 0.57 | 0.70 |
| Cancer drug use | 1.45 | <0.001 | 1.22 | 1.72 |
| Total number of different drugs[4] | 1.03 | <0.001 | 1.02 | 1.03 |

[1]Amisulpride omitted, too few subjects
[2]Residential Aged Care Facility
[3] Dispensing partly in the community and partly in RACF
[4]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

All study drugs except thioridazine had significant ORs of death in this model. The ORs chlorpromazine and haloperidol were significantly increased compared with all single study drugs. This was consistent with the results from the Cox regressions. Trifluoperazine, carbamazepine and valproate were associated with significantly increased ORs. However, in the Cox regression model these drugs were associated with a significant RR less than 1 (that is lower risk compared with olanzapine reference group). The OR for risperidone was significantly increase when compared with the OR for pericyazine.

## 3.1.6 Post-Hoc Interactions

Interactions for age, gender and diuretic use for each study drug are displayed in Table 2 Appendix 4. The comparative RR were then established and are displayed in Table 14. Amisulpride, thioridazine, trifluoperazine and mixed groups were omitted as there were less than 20 subjects in some groups.

*Table 14. Significant Relative Risk for internal drug group comparisons with age, sex and diuretic use combinations [1,2]*

| Drug | Group | Factor varied | Comparison RR | 1-tailed p values | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| Halo-peridol | Old/Male/Diuretic vs Old/Female/Diuretic | Gender | 1.51 | <0.001 | 1.27 | 1.79 |
| | Old/Male/Non-Diuretic vs. Old/Female/Non-diuretic | Gender | 1.42 | <0.001 | 1.20 | 1.68 |
| | Young/Male/Diuretic vs. Young/Female/Diuretic | Gender | 1.43 | <0.001 | 1.16 | 1.77 |
| | Young/Male/Non-Diuretic vs. Young/Female/Non-Diuretic | Gender | 1.75 | <0.001 | 1.41 | 2.18 |
| | Old/Male/Diuretic vs. Old/Male/Non-Diuretic | Diuretic | 1.18 | 0.013 | 1.02 | 1.37 |
| | Young/Male/Diuretic vs. Young/Male/NonDiuretic | Diuretic | 1.19 | 0.020 | 1.01 | 1.41 |
| | Young/Female/Diuretic vs. Young/Female/Non-Diuretic | Diuretic | 1.46 | 0.002 | 1.13 | 1.89 |
| Olan-zapine | Old/Male/Diuretic vs Old/Female/Diuretic | Gender | 1.48 | 0.010 | 1.06 | 2.05 |
| | Old/Male/Non-Diuretic vs. Old/Female/Non-Diuretic | Gender | 1.54 | 0.002 | 1.14 | 2.07 |
| | Young/Diuretic/Male vs. Young/Diuretic/Female | Gender | 2.01 | 0.009 | 1.13 | 3.56 |
| | Old/Male/Diuretic vs Young/Male/Diuretic | Age | 1.52 | 0.014 | 1.05 | 2.21 |
| | Old/Female/Diuretic vs Young/Female/ Diuretic | Age | 2.07 | 0.004 | 1.2 | 3.57 |
| Peri-cyazine | Old/Male/Diuretic vs. Old/Male/Non-Diuretic | Diuretic | 1.86 | 0.002 | 1.22 | 2.84 |
| | Old/Female/Diuretic vs. Old/Female/Non-Diuretic | Diuretic | 2.22 | 0.003 | 1.26 | 3.92 |
| Queti-apine | Old/Male/Non-Diuretic vs. Young/Male/Non-Diuretic | Age | 2.46 | 0.010 | 1.15 | 5.27 |
| Risperi-done | Old/Male/Diuretic vs Old/Female/Diuretic | Gender | 1.57 | 0.011 | 1.07 | 2.33 |
| | Old/Male/Non-Diuretic vs. Old/Female/Non-Diuretic | Gender | 1.69 | 0.003 | 1.16 | 2.45 |
| | Young/Male/Non-Diuretic vs. Young/Female/Non-Diuretic | Gender | 2.57 | 0.002 | 1.37 | 4.84 |
| | Old/Female/Non-Diuretic vs. Young/Female/Non-Diuretic | Age | 2.26 | 0.005 | 1.22 | 4.19 |
| Carbama-zepine | Old/Female/Diuretic vs. Old/Female/Non-Diuretic | Diuretic | 2.82 | 0.003 | 1.35 | 5.89 |
| | Young/Male/Diuretic vs. Young/Male/NonDiuretic | Diuretic | 1.71 | 0.004 | 1.15 | 2.54 |
| | Young/Female/Diuretic vs. Young/Female/Non-Diuretic | Diuretic | 1.89 | 0.018 | 1.05 | 3.42 |
| | Old/Male/Non-Diuretic vs Old/Female/Non-Diuretic | Gender | 3.15 | 0.001 | 1.53 | 6.5 |

| | | | | | |
|---|---|---|---|---|---|
| Young/Male/Non-Diuretic vs. Young/Female/Non-Diuretic | Gender | 1.81 | 0.016 | 1.05 | 3.09 |
| Old/Male/Non-Diuretic vs. Young/Male/Non-Diuretic | Age | 1.71 | 0.007 | 1.11 | 2.62 |

[1]Amisulpride, thioridazine, trifluoperazine and mixed groups omitted.
[2]No significant interactions for chlorpromazine or valproate

Male gender was associated with a significantly increased RR in all of the haloperidol groups and three of the olanzapine and risperidone groups. Diuretic use was associated with increased RR in three haloperidol groups and older pericyazine subjects. Age was associated with a significantly increased RR in olanzapine subjects who were dispensed a diuretic. Carbamazepine groups were generally associated with a reduced RR compared with the young, female, non-diuretic using olanzapine subjects. Thus the comparative RR for carbamazepine need to be viewed in the light of Table 2 Appendix 4. There were no significant interactions for chlorpromazine or valproate

### 3.1.7 Admission for fractured femur in NSW and ACT residents in 2003 and 2004

Subjects were classified by their residential postcode. Those residing in NSW and ACT were considered in a sub-analysis using a Cox regression model with admission for fractured femur in 2003 or 2004 as the end point. Matched deidentified public hospital admissions with a primary diagnosis of fractured femur in 2003 and 2004 were extracted from NSW and ACT public hospital service data. Matched deidentified private hospital admissions with the primary diagnosis of fractured femur were extracted from the national private hospital service data. Those with admission for fractured femur to a private hospital with a residential postcode in NSW and ACT were then selected.

There were 407 admissions for fractured femur for incident antipsychotic, carbamazepine and valproate subjects in NSW and ACT public and private hospitals. Two hundred and eighteen of these admissions occurred after the index dispensing of the study drug. Of these admissions, 179 occurred in subjects who started a second study drug, and hence were censored at the point of starting the second drug. A survival analysis was performed using 88 admissions for fractured femur. Table 15 displays the covariates with a partial p value <0.05 associated with admission for fractured femur in the NSW and ACT incident cohort.

*Table 15. Significant covariates associated with admission for fractured femur in incident antipsychotic, carbamazepine and valproate subjects in NSW and ACT hospitals in 2003 and 2004[1]*

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Carbamazepine | 0.36 | 0.012 | 0.16 | 0.80 |
| Valproate | 0.43 | 0.007 | 0.24 | 0.79 |
| Age | 1.10 | <0.001 | 1.06 | 1.15 |
| Mixed[2] (high) vs Community | 2.04 | 0.016 | 1.15 | 3.64 |
| Beta blockers | 0.51 | 0.019 | 0.29 | 0.90 |

[1]Olanzapine was the reference group
[2] Dispensing partly in the community and partly in RACF

Thus carbamazepine and valproate use was associated with a significantly reduced Relative Risk for admission with fractured femur compared with olanzapine subjects. Age and changing residential status were also, unsurprisingly, predictors. The sample contained too

few admissions for fractured femur for this method of analysis to exclude a real association between falls resulting in fractured femur and a study drug. This analysis was consistent with the main analysis, and subjects who were dispensed a second study drug were censored as alive. This methodological approach excluded 179 admissions for fractured femur.

### 3.1.8 Admission for stroke in NSW and ACT residents in 2003 and 2004

Subjects were classified by postcode and those residing in NSW and ACT were considered in a sub-analysis using a Cox regression model with admission for stroke in 2003 or 2004 as the end point. Matched deidentified public hospital admissions with a primary diagnosis of stroke in 2003 and 2004 were extracted from NSW and ACT public hospital service data. Matched deidentified private hospital admissions with the primary diagnosis of stroke were extracted from the national private hospital service data. Those with admission for stroke to a private hospital with a residential postcode in NSW and ACT were then selected. International Classification of Diseases, 10th Revision, codes for stroke were chosen on the basis of a previous validation study[113]. The codes extracted were: H34.1 Central retinal artery occlusion, I63.x Cerebral infarction, I64.x Stroke, not specified as haemorrhage or infarction, I61.x Intracerebral haemorrhage, I60.x Subarachnoid haemorrhage). Transient ischaemic attacks (TIA) were not extracted as TIAs may not result in a hospital admission and are associated with more diagnostic uncertainty.

There were 331 admissions for stroke, with 141 occurring on or after the date of first dispensing of the study drug. Study subjects had commenced a second study drug prior to the 121 admissions. There were only 57 admissions available for analysis. Significant covariates associated with admission for stroke are displayed in Table 16.

*Table 16. Significant covariates associated with admission for stroke in incident antipsychotic, carbamazepine and valproate subjects in NSW and ACT in 2003 and 2004*[1]

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Mixed[2] (high) vs Community | 3.05 | 0.002 | 1.53 | 6.06 |
| Calcium channel blockers | 2.07 | 0.006 | 1.23 | 3.49 |
| Glycosides | 2.28 | 0.005 | 1.29 | 4.02 |

[1]Olanzapine was the reference group

[2] Dispensing partly in the community and partly in RACF

There were no drug groups significantly associated with admission for stroke in this sample. However the number of strokes was small (N=57) and 121 strokes occurred in subjects who had commenced a second study drug. As risk factors for stroke include hypertension and atrial fibrillation, the association of calcium channel blocker and glycoside use with stroke was not surprising. It is plausible that stroke was the event leading to permanent or temporary residence in an Aged Care Facility. There were insufficient strokes to exclude an association with any of the study drugs.

## 3.2 PREVALENT ANTIPSYCHOTIC, CARBAMAZEPINE AND VALPROATE SUBJECTS

In 2003 and 2004 there were 9831 prevalent antipsychotic, carbamazepine or valproate users among the DVA entitled beneficiaries 65 years and older. Fifty-five percent of subjects were male. One third resided in an Aged Care Facility on 1st January, 2003. However, 56% were resident in an Aged Care Facility at some point in 2003 or 2004. Twenty-four percent of the sample had died by 31.12.04. The age distribution of the subjects is given in Table 1.

*Table 1. Age distribution of prevalent antipsychotic, carbamazepine and valproate subjects at 1.1.03*

| Age in years at 2003 | N | Percentage |
|---|---|---|
| 65-69 | 245 | 2% |
| 70-74 | 612 | 6% |
| 75-79 | 2823 | 29% |
| 80-84 | 3701 | 38% |
| 85-89 | 1809 | 18% |
| 90-94 | 507 | 5% |
| 95-99 | 121 | 1% |
| 100+ | 13 | 0% |

There were sufficient subjects to analyse data for five conventional antipsychotic drugs, five atypical antipsychotic drugs, and two anti-epileptic drugs, carbamazepine and valproate. There were only two subjects taking clozapine, an atypical antipsychotic drug. Both were taking other antipsychotic drugs and hence are included in the mixed column. Those who were dispensed two study drugs at 1.1.03 were entered into the mixed group. Prevalent users who were subsequently started on a second study drug were included in the first drug group and censored as alive at the point of starting the second drug. All descriptive characteristics, psychotropic medication dispensing and dispensing of other medication were significantly different across the study drug groups given the large sample ($p<0.001$). All variables presented (except anticholinergic drug dispensing) were used as covariates in the Cox regression and logistic regression models. The average age, percentage male and residential status of each drug group is displayed in Table 2.

*Table 2. Prevalent antipsychotic, carbamazepine and valproate subjects by age, sex and place of residence in 2003 and 2004*

| | N | Mean age | Percentage Male | Community | RACF[1] | Mixed[2] |
|---|---|---|---|---|---|---|
| Conventional AP drug | | | | | | |
| Chlorpromazine | 284 | 80.92 | 51% | 60% | 36% | 4% |
| Haloperidol | 1114 | 83.32 | 52% | 27% | 67% | 5% |
| Pericyazine | 710 | 83.47 | 55% | 32% | 61% | 7% |
| Thioridazine | 167 | 81.12 | 56% | 63% | 34% | 4% |
| Trifluoperazine | 317 | 79.93 | 44% | 79% | 16% | 5% |
| Atypical AP drugs | | | | | | |
| Amisulpride | 16 | 78.53 | 63% | 56% | 38% | 6% |
| Olanzapine | 2249 | 82.38 | 50% | 32% | 60% | 9% |
| Quetiapine | 204 | 80.95 | 53% | 42% | 50% | 8% |
| Risperidone | 993 | 82.65 | 49% | 25% | 68% | 7% |
| Others | | | | | | |
| Carbamazepine | 1734 | 80.52 | 62% | 80% | 15% | 5% |
| Valproate | 1956 | 80.71 | 60% | 61% | 30% | 9% |
| Mixed | 87 | 78.98 | 53% | 39% | 52% | 9% |

[1]Residential Aged Care Facility
[2]Some dispensing occurred in the community and some in RACF

Carbamazepine (80%), trifluoperazine (79%), thioridazine (63%), valproate (61%) and chlorpromazine (60%) had the highest percentage of subjects receiving all dispensings in the community. For each drug, apart from "mixed", the percentage with dispensing that occurred entirely in the community was less for the prevalent cohort than the incident cohort. Entry (or exit) from a residential aged care facility occurred in 10% of the mixed group, 9% of the olanzapine and valproate groups, 8% of the quetiapine group and 7% of the pericyazine and risperidone groups.

The pattern of psychotropic medication dispensing is contained in Table 3. Antihistamine use does not include antihistamine medications bought without a prescription. The use of cholinesterase inhibitors varied among the drug groups, with 26% of quetiapine subjects receiving a cholinesterase inhibitor at some point in 2001 through 2004.

*Table 3. Prevalent antipsychotic, carbamazepine and valproate subjects by dispensing of other classes of psychotropic medications in 2003 and 2004*

| | Antidepressant use | Lithium use | BZDP use | Cholinesterase Inhibitor use | Antihistamine use |
|---|---|---|---|---|---|
| Conventional AP drug | | | | | |
| Chlorpromazine | 55% | 5% | 60% | 5% | 20% |
| Haloperidol | 41% | 1% | 62% | 13% | 9% |
| Pericyazine | 47% | 1% | 57% | 11% | 8% |
| Thioridazine | 41% | 5% | 51% | 7% | 14% |
| Trifluoperazine | 49% | 2% | 58% | 4% | 18% |
| Atypical AP drugs | | | | | |
| Amisulpride | 63% | 6% | 69% | 6% | 6% |
| Olanzapine | 52% | 4% | 58% | 14% | 8% |
| Quetiapine | 53% | 3% | 62% | 26% | 11% |
| Risperidone | 46% | 2% | 54% | 15% | 9% |
| Others | | | | | |
| Carbamazepine | 39% | 1% | 48% | 3% | 18% |
| Valproate | 46% | 1% | 49% | 6% | 13% |
| Mixed | 33% | 7% | 53% | 11% | 8% |

The pattern of selected medical drug dispensing for the subjects is displayed in Table 4. Like the incident cohort, the prevalence of dispensing for anti-epileptic drugs was higher in the carbamazepine and valproate subjects. The small number of subjects in the amisulpride group (N=16) may limit the significance of the associated dispensing. Morphine use increased in the prevalent cohort compared with the incident cohort for pericyazine (15% to 20%), thioridazine (5% to 10%), olanzapine (12% to 16%), quetiapine (5% to 18%), risperidone (12% to 18%) and mixed (11% to 16%), with small increases for both carbamazepine and valproate. Prevalent chlorpromazine and haloperidol subjects were less likely to be dispensed morphine than incident haloperidol and chlorpromazine subjects. There was a general reduction in the use of anti-cancer drugs in the prevalent cohort compared with the incident cohort, though this was most marked for haloperidol and chlorpromazine subjects.

*Table 4. Prevalent antipsychotic, carbamazepine and valproate subjects by dispensing of selected classes of medications in 2003 and 2004*

| | Diuretic use | Glycoside use | Anti-epileptic drug use[1] | Morphine use | Coxib use | Oncological drug use |
|---|---|---|---|---|---|---|
| Conventional AP drugs | | | | | | |
| Chlorpromazine | 42% | 11% | 4% | 12% | 30% | 6% |
| Haloperidol | 35% | 14% | 4% | 21% | 20% | 4% |
| Pericyazine | 34% | 11% | 3% | 20% | 21% | 3% |
| Thioridazine | 36% | 12% | 3% | 10% | 26% | 3% |
| Trifluoperazine | 38% | 12% | 2% | 6% | 40% | 3% |
| Atypical AP drugs | | | | | | |
| Amisulpride | 56% | 13% | 13% | 31% | 13% | 6% |
| Olanzapine | 35% | 12% | 4% | 16% | 21% | 3% |
| Quetiapine | 32% | 8% | 2% | 18% | 29% | 4% |
| Risperidone | 36% | 12% | 5% | 18% | 18% | 4% |
| Others | | | | | | |
| Carbamazepine | 45% | 14% | 14% | 11% | 31% | 6% |
| Valproate | 43% | 15% | 15% | 12% | 28% | 6% |
| Mixed | 37% | 15% | 8% | 11% | 22% | 5% |

[1]Anti-epileptic drugs excluding carbamazepine, valproate and clonazepam

The use of drugs for some movement disorders is detailed in Table 5. Quetiapine and, to some extent, olanzapine, were more frequently dispensed to those who presumably had Parkinson's disease. It was hypothesised that anticholinergic drugs dispensed in the absence of drugs for Parkinson's disease may be a marker for extra-pyramidal side effects. Trifluoperazine was associated with increased dispensing of anticholinergic medication in the absence of other drugs used in Parkinson's disease. The small size of the amisulpride group (N=16) limits the importance that can be given to the increased dispensing of anticholinergic medication associated with this drug. However, it is consistent with the findings for the incident amisulpride group (N=48, 6% using anticholinergic drugs without other drugs to treat Parkinson's disease).

Table 5. Prevalent antipsychotic, carbamazepine and valproate subjects by dispensing of drugs used in movement disorders in 2003 and 2004

| | Drugs used in Parkinson's disease[1] | Anticholinergic drugs | Anticholinergic drugs without other drugs for Parkinson's Disease |
|---|---|---|---|
| Conventional AP drugs | | | |
| Chlorpromazine | 7% | 4% | 2% |
| Haloperidol | 5% | 4% | 4% |
| Pericyazine | 6% | 2% | 2% |
| Thioridazine | 8% | 2% | 2% |
| Trifluoperazine | 4% | 12% | 11% |
| Atypical AP drugs | | | |
| Amisulpride | 25% | 13% | 6% |
| Olanzapine | 11% | 2% | 2% |
| Quetiapine | 24% | 6% | 4% |
| Risperidone | 8% | 5% | 4% |
| Others | | | |
| Carbamazepine | 4% | 1% | 1% |
| Valproate | 9% | 1% | 1% |
| Mixed | 7% | 2% | 2% |

[1]Excluding anti-cholinergic drugs

The total number of drugs in the 12 month period prior to the index dispensing of antipsychotic, carbamazepine and valproate medication was extracted for each subject and the mean for each drug established. The results are displayed in Table 6. There was an increase in the average total number of drugs in the 12 month period for all drug groups. The largest increases were seen in the pericyazine group (10.00 to 12.05), trifluoperazine (10.58 to 13.46), amisulpride (10.54 to 16.13), olanzapine (10.63 to 13.19) and mixed (10.29 to 13.78).

*Table 6. Prevalent antipsychotic, carbamazepine and valproate subjects by mean of different drug count in the year preceding first dispensing in 2003 or 2004*

| | N | Average total number of different drugs in 12 months |
|---|---|---|
| Conventional AP drugs | | |
| Chlorpromazine | 284 | 14.28 |
| Haloperidol | 1114 | 13.46 |
| Pericyazine | 710 | 12.05 |
| Thioridazine | 167 | 11.72 |
| Trifluoperazine | 317 | 13.46 |
| Atypical AP drugs | | |
| Amisulpride | 16 | 16.13 |
| Olanzapine | 2249 | 13.19 |
| Quetiapine | 204 | 14.82 |
| Risperidone | 993 | 12.56 |
| Others | | |
| Carbamazepine | 1734 | 14.81 |
| Valproate | 1956 | 14.74 |
| Mixed | 87 | 13.78 |

*Table 7. Prevalent antipsychotic, carbamazepine and valproate drug users by death per 1000 people years of drug exposure in 2003 or 2004[1,2]*

| | N | Alive[1] | Death during exposure[2] | Deaths per 1000 person years of exposure | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| Conventional AP drugs | | | | | | |
| Chlorpromazine | 284 | 90% | 10% | 79 | 52 | 115 |
| Haloperidol | 1114 | 78% | 22% | 243 | 213 | 275 |
| Pericyazine | 710 | 82% | 18% | 164 | 137 | 195 |
| Thioridazine | 167 | 90% | 10% | 95 | 56 | 153 |
| Trifluoperazine | 317 | 93% | 7% | 53 | 33 | 81 |
| Atypical AP drugs | | | | | | |
| Amisulpride | 16 | 100% | 0% | 0 | | |
| Olanzapine | 2249 | 80% | 20% | 167 | 152 | 183 |
| Quetiapine | 204 | 83% | 17% | 152 | 105 | 212 |
| Risperidone | 993 | 78% | 22% | 200 | 174 | 229 |
| Others | | | | | | |
| Carbamazepine | 1734 | 93% | 7% | 52 | 43 | 62 |
| Valproate | 1956 | 88% | 12% | 96 | 84 | 109 |
| Mixed | 87 | 71% | 29% | 186 | 120 | 274 |

[1]Subjects were considered alive if they were alive when starting a second study drug, were alive 60 days after discontinuation of a study drug, or alive on 31.12.04.

[2]Death was considered to have occurred during the drug exposure if the death occurred up to 60 days after the last date of drug dispensing.

Death per 1000 person years at risk (pyar) is displayed in Table 7. The death rates for the prevalent cohort were lower than in the incident cohort for every group except thioridazine (76 to 95 deaths per 1000 pyar). Haloperidol again has the highest mortality rate in the prevalent sample, however, the second highest mortality rate occurred in the risperidone group. There was evidence that the haloperidol death rate was higher than all other study drugs ($p<0.05$), except for risperidone and the mixed group. Chlorpromazine had a mortality rate of 483 deaths per 1000 pyar in the incident group, tand only 79 deaths per 1000 pyar in the prevalent cohort.

## 3.2.1 Kaplan-Meier Survival Curves and Log Rank Tests

Survival curves were plotted for prevalent antipsychotic, carbamazepine or valproate users. As stated in the methodology, subjects who commenced a second study drug were considered alive from the point of commencing the second drug. Subjects who discontinued the medication were followed for 60 days after the last dispensing and then censored as alive.

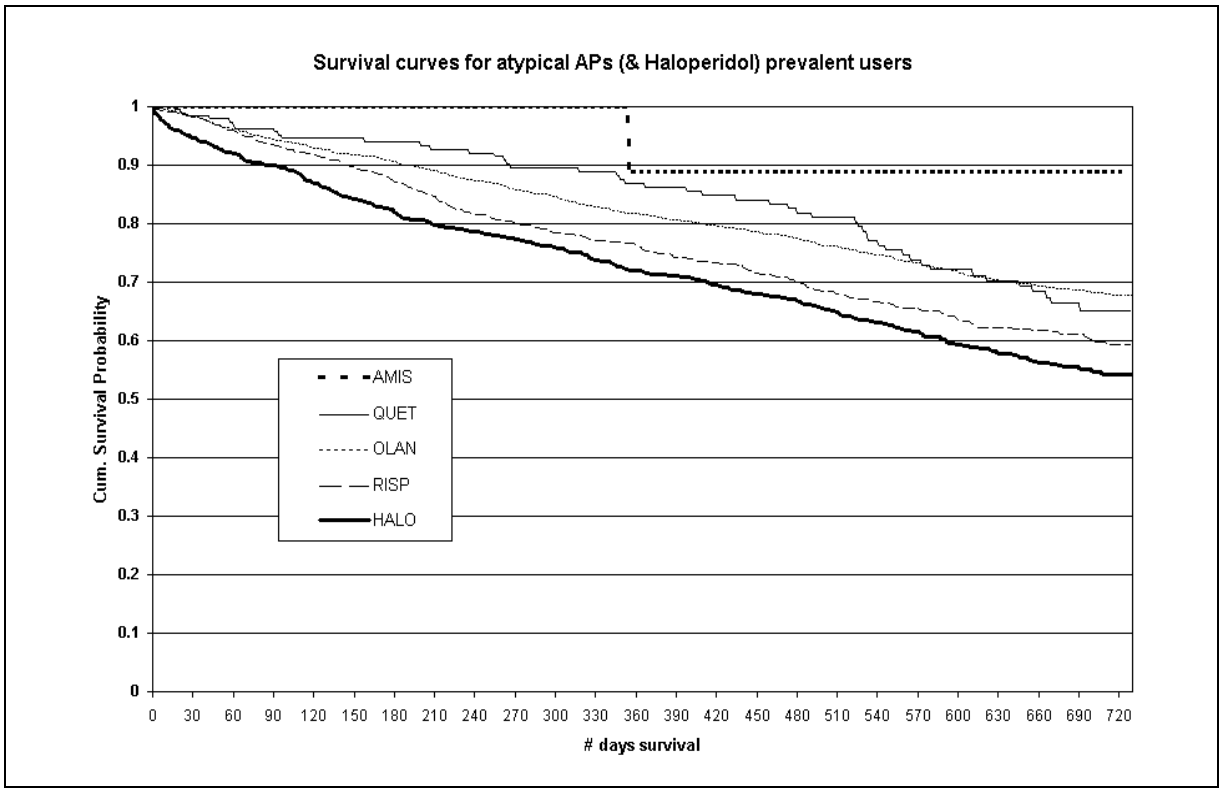



*Figure 1 Survival curves for atypical antipsychotic drugs (with haloperidol added for comparison) in prevalent antipsychotic subjects*

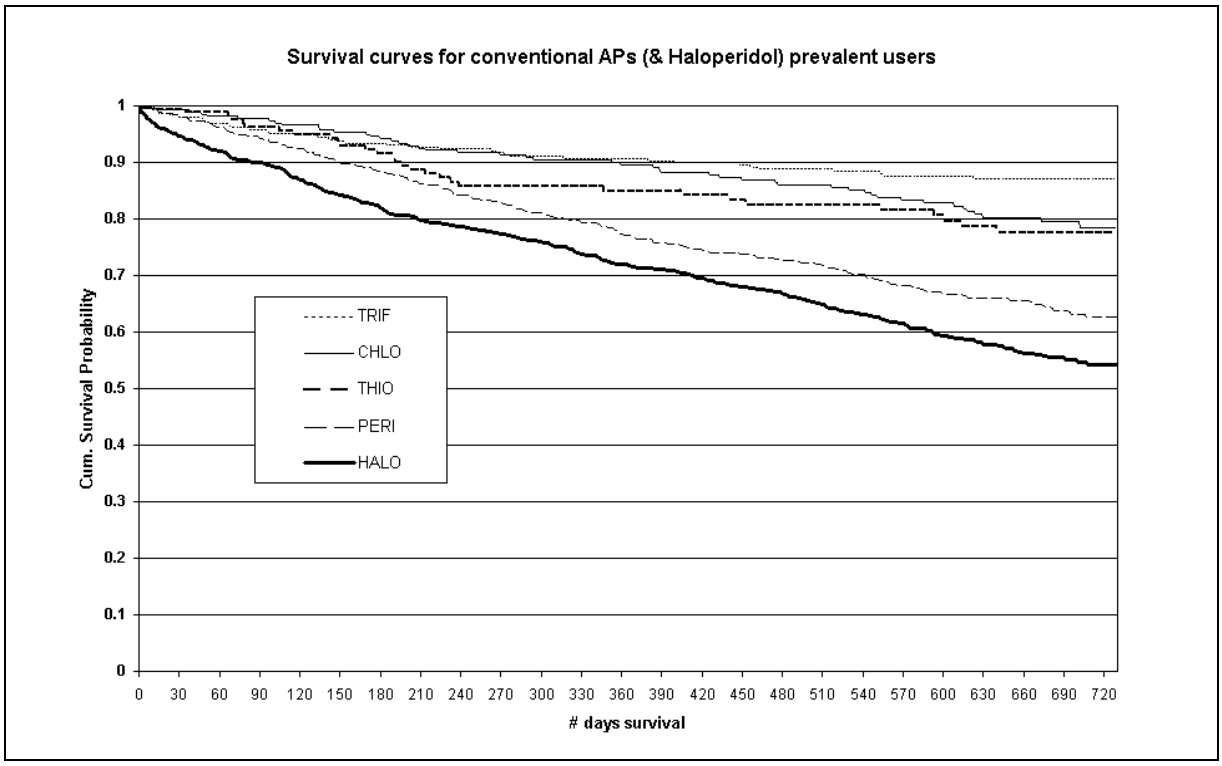



*Figure 2. Survival curves for conventional antipsychotic drugs in prevalent antipsychotic subjects*

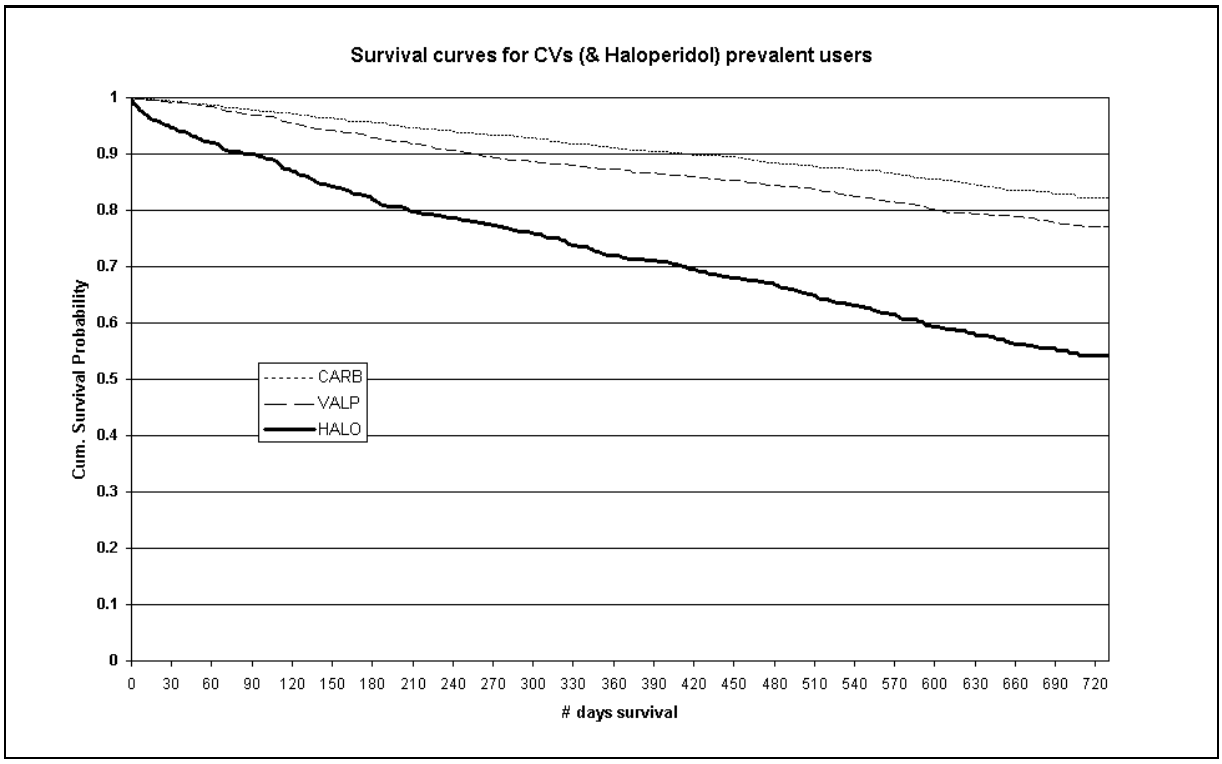



*Figure 3. Survival curves for carbamazepine and valproate (with haloperidol added for comparison) in prevalent haloperidol, carbamazepine or valproate users*

*Table 8. Log Rank Tests for survival curves in prevalent antipsychotic, carbamazepine or valproate subjects*

| Model | Statistic | df | p-value |
|---|---|---|---|
| All 12 AP, CV (Incl. Mult) | 398.18 | 11 | <0.001 |
| Atypical (4) | 21.03 | 3 | <0.001 |
| Conventional (4) | 56.37 | 3 | <0.001 |
| CV (2) | 14.7 | 1 | <0.001 |

The Log Rank test for all twelve drugs (including the mixed group), with 11 degrees of freedom, was highly significant ($p<0.001$). Haloperidol was then removed from the analysis and drugs analysed in groups to ascertain if differences in survival for the remaining drug groups were significant. Differences in survival among the atypical antipsychotic medication group were significant, with risperidone associated with poorer outcome. The differences in the conventional group was also significant, with pericyazine being associated with a poorer outcome. The survival curves for prevalent chlorpromazine users indicated better survival rates compared with incident chlorpromazine subjects. The haloperidol survival curve in prevalent subjects demonstrated a poorer outcome compared with other study drugs. The haloperidol survival curve was included in the graphs for comparison but was not included in the Log Rank tests for the sub-groups. Compared with the survival curve in incident haloperidol subjects, the curve for prevalent haloperidol subjects had a relatively constant gradient. Both prevalent and incident carbamazepine and valproate users had better outcomes than other study drug subjects.

## 3.2.2 Strength Survival Curves and Log Rank tests in prevalent subjects

Individual antipsychotic drugs were considered by their formulation, that is by strength, oral solution and short-acting parenteral forms. As stated previously depot medications were

excluded. There were only significant differences in the survival curves among the various formulations for olanzapine, risperidone and haloperidol formulations. Formulations of olanzapine and risperidone with too few subjects were removed and the Log Rank tests run using the remaining groups. The prevalent haloperidol subjects dispensed the drug as an oral solution or in a parenteral form had a poor outcome. The haloperidol strengths 0.5mg, 1.5mg and 5mg were tested against each other. The results of these Log Rank tests are presented in Table 9.

*Table 9. Log Rank tests for reduced prevalent haloperidol, olanzapine and risperidone groups*

| | N | Log Rank Statistic | df | p-value |
|---|---|---|---|---|
| Haloperidol 0.5mg | 721 | 10.1 | 2 | <0.001 |
| Haloperidol 1.5mg | 130 | | | |
| Haloperidol 5mg | 52 | | | |
| Olanzapine 2.5mg | 653 | 0.02 | 1 | 0.88 |
| Olanzapine 5mg | 732 | | | |
| Risperidone 1mg | 760 | 0.2 | 1 | 0.66 |
| Risperidone 2mg | 79 | | | |

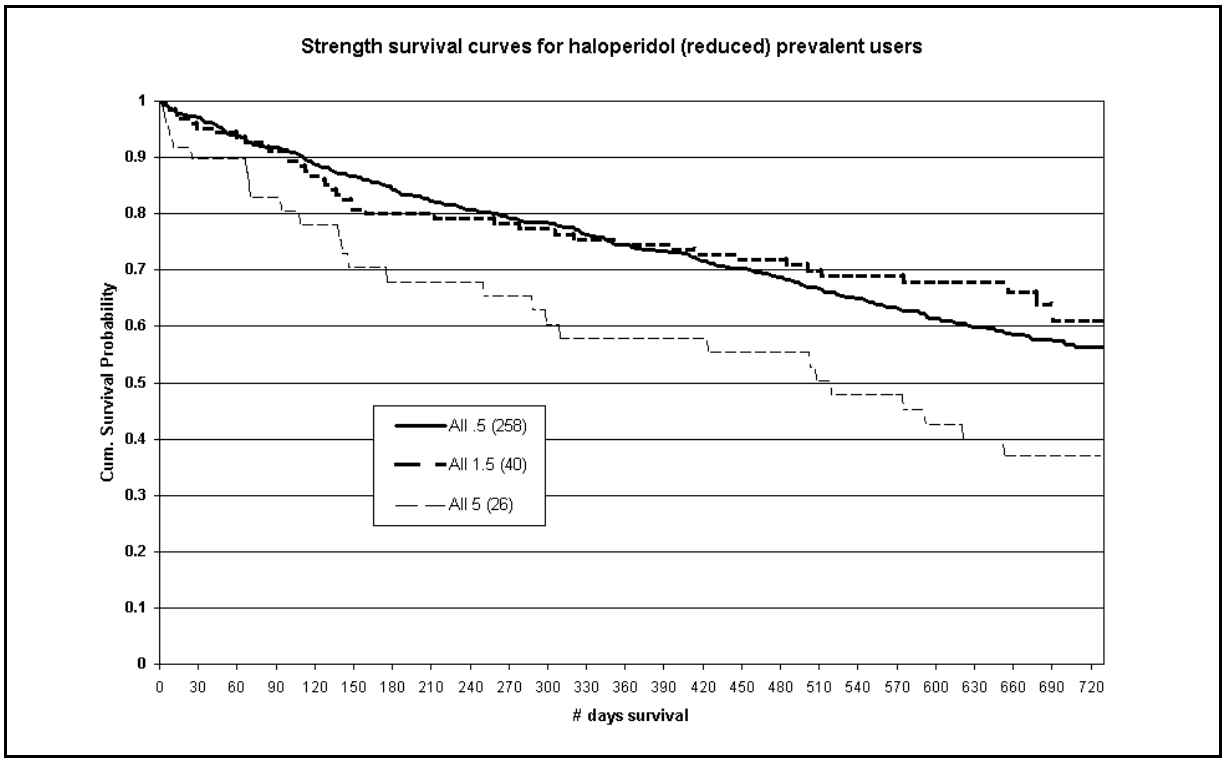
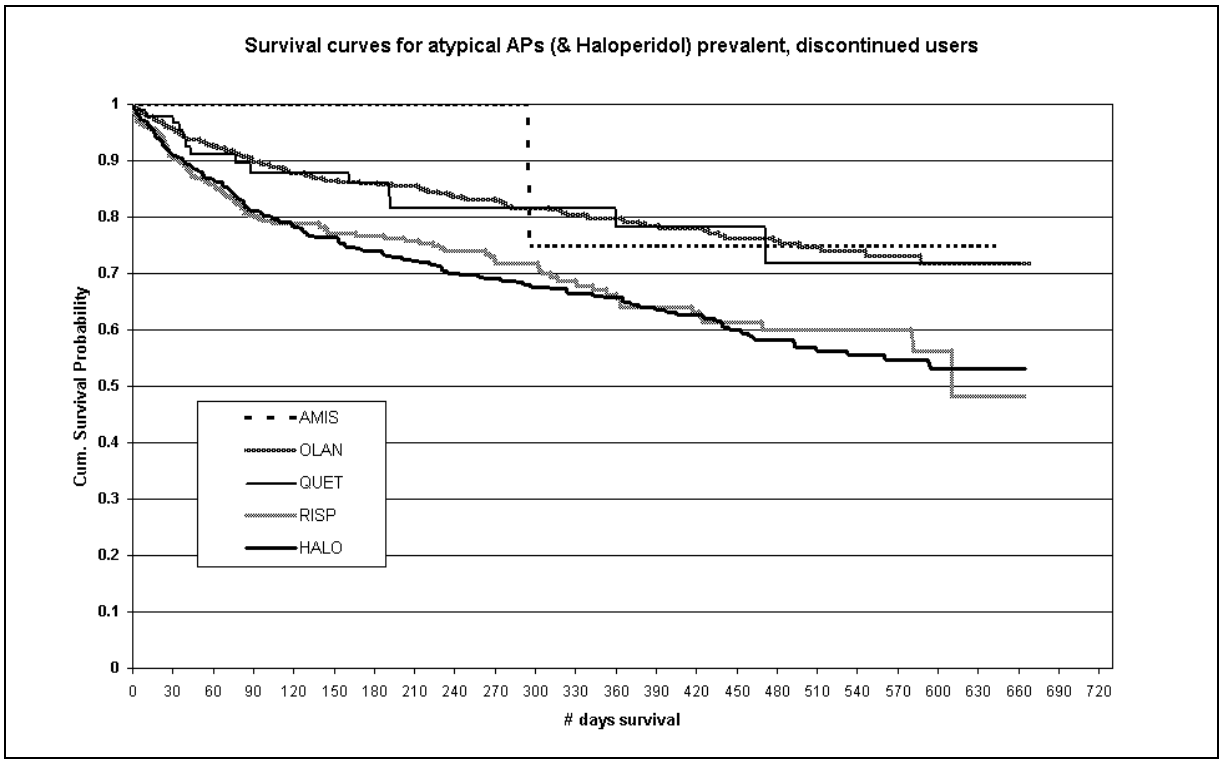



*Figure 6. Reduced strength survival curves for prevalent haloperidol users*

Thus only prevalent haloperidol subjects had a significant differences in survival curves for different strengths. Haloperidol 5mg was associated with a significantly poorer outcome than haloperidol 1.5mg and haloperidol 0.5mg in prevalent subjects. This contrasts with the findings for incident haloperidol subjects, where haloperidol 1.5mg and haloperidol 5mg were associated with poorer outcomes compared with haloperidol 0.5mg.

### 3.2.3 Survival curves for prevalent subjects discontinuing antipsychotic medication




[1]Amisulpride has been deleted from the graph (N=9)

*Figure 7. Survival Curves for prevalent atypical antipsychotic subjects who discontinued antipsychotic medication (haloperidol included for comparison)[1]*

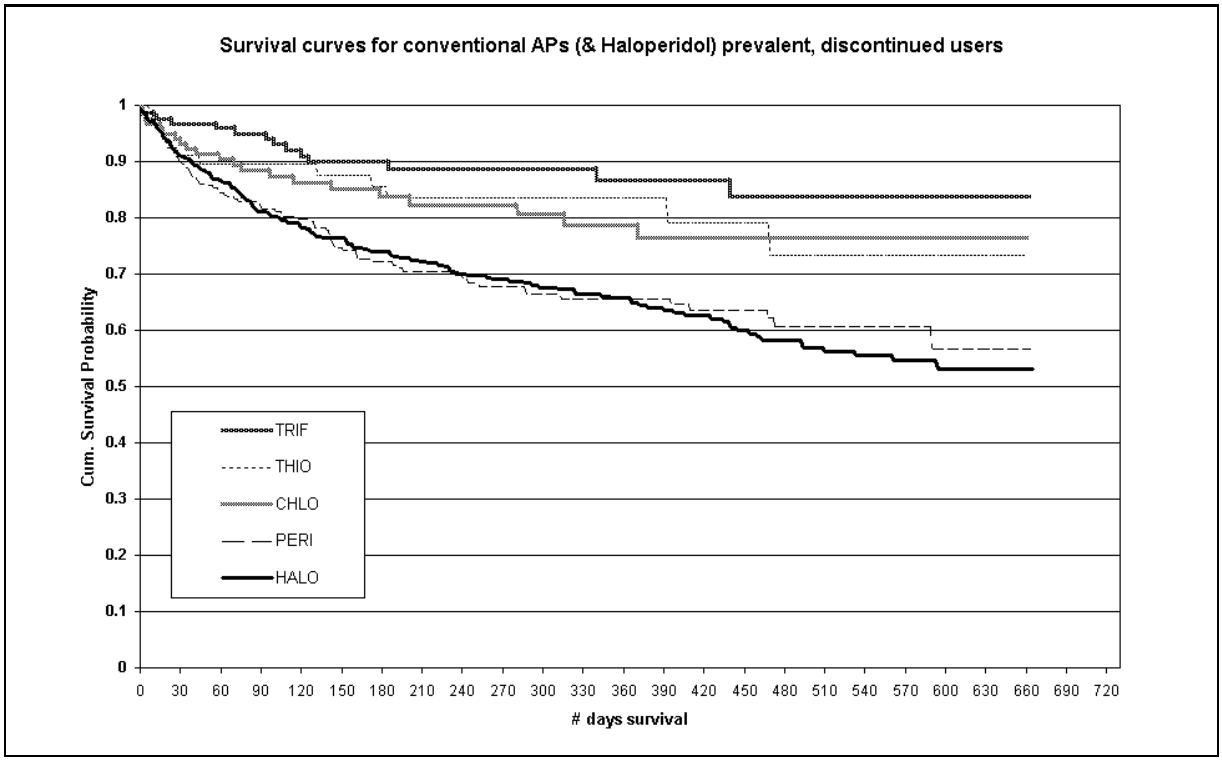



*Figure 8. Survival Curves for prevalent conventional antipsychotic subjects who discontinued antipsychotic medication*

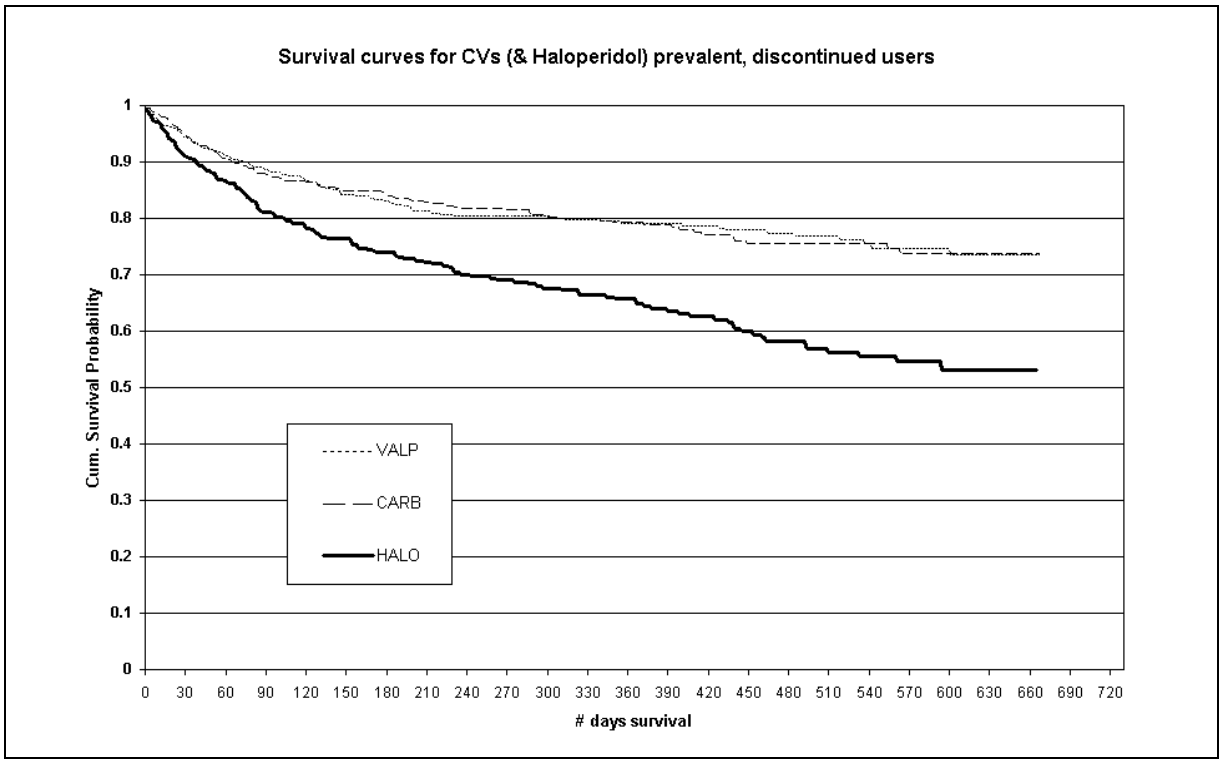



*Figure 9. Survival Curves for prevalent carbamazepine and valproate subjects who discontinued antipsychotic medication (haloperidol included for comparison)*

The risperidone (N=433), pericyazine (N=332) and haloperidol (N=538) curves for prevalent subjects who discontinued the study medication were similar.

## 3.2.4 Survival Analysis for prevalent subjects

### 3.2.4.1 Survival Analysis to 31.12.04

The Relative Risk (RR) of death until 31.12.04. was established using a multivariate Cox Regression. The results from the final model are displayed in Table 10. Variables with a partial p value < 0.05 have been presented. Prevalent olanzapine subjects were chosen as the reference group, hence the relative risks presented are with respect to the prevalent olanzapine group.

The RR for prevalent haloperidol, risperidone, and the mixed groups were similar to that found in the incident analysis. However, chlorpromazine was no longer associated with a significantly raised RR and valproate was no longer associated with a significantly lower RR. In the prevalent sample, the RR of death associated with morphine use was significant but lower compared with the incident analysis. Diuretic and cancer drug use were no longer significant predictors.

*Table 10. Relative risk of death until 31.12.04. with olanzapine subjects as the reference group in prevalent antipsychotic, carbamazepine and valproate subjects*[1]

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Haloperidol | 1.38 | <0.001 | 1.23 | 1.54 |
| Risperidone | 1.24 | <0.001 | 1.10 | 1.41 |
| Carbamazepine | 0.79 | 0.001 | 0.69 | 0.91 |
| Multiple study drugs | 1.49 | 0.029 | 1.04 | 2.13 |
| Sex (Males high) | 1.76 | <0.001 | 1.61 | 1.91 |
| Age | 1.05 | <0.001 | 1.04 | 1.05 |
| RACF[2] vs Community | 1.97 | <0.001 | 1.78 | 2.18 |
| Antidepressants | 0.76 | <0.001 | 0.69 | 0.82 |
| Lithium | 0.58 | 0.010 | 0.39 | 0.88 |
| Antihistamines | 0.61 | <0.001 | 0.53 | 0.72 |
| Antihypertensives | 0.76 | 0.039 | 0.58 | 0.99 |
| Antithrombotics | 0.76 | <0.001 | 0.70 | 0.83 |
| Calcium channel blockers | 0.80 | <0.001 | 0.71 | 0.90 |
| Glycosides | 1.13 | 0.044 | 1.00 | 1.26 |
| Lipid reducers | 0.73 | <0.001 | 0.64 | 0.83 |
| Morphine use | 2.77 | <0.001 | 2.52 | 3.03 |
| Coxib use | 0.74 | <0.001 | 0.66 | 0.82 |
| Total number of different drugs[3] | 1.05 | <0.001 | 1.04 | 1.05 |

[1]Prevalent olanzapine subjects as the reference group
[2]Residential Aged Care Facility
[3]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

## 3.2.5 Case Control Analysis of prevalent antipsychotic, carbamazepine and valproate subjects

The results from the logistic regression comparing exposure to drugs over a sixty day study period are displayed in Table 11. The sixty day study period was either the sixty days prior to death or sixty days prior to a randomised study date. Olanzapine was not used as a reference group in this analysis. The reference group was formed by those not using a study drug in the study period. Amisulpride, chlorpromazine and the multiple study drug group data were excluded from the analysis as the subject numbers were too small. Lithium was not used as a covariate as there were insufficient subjects dispensed the drug.

Haloperidol, olanzapine, pericyazine, risperidone and valproate had significantly increased ORs of death. The haloperidol OR of death was significantly higher than the ORs associated with olanzapine, quetiapine, thioridazine and trifluoperazine ($p<0.05$). Quetiapine was not associated with an increased OR of death. Covariates associated with an increased OR were male gender, age, residence in an Aged Care facility for the period of dispensing, drugs used for Parkinson's disease (excluding anti-cholinergic drugs) and morphine use.

*Table 11. Odds Ratios of death from the case control study of drug exposure 60 days prior to date of death or a randomised study date in prevalent antipsychotic, carbamazepine or valproate subjects*

| Predictor | OR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Haloperidol | 9.04 | <0.001 | 6.40 | 12.75 |
| Olanzapine | 3.85 | <0.001 | 2.61 | 5.69 |
| Pericyazine | 3.65 | <0.001 | 1.87 | 7.12 |
| Risperidone | 4.85 | <0.001 | 2.97 | 7.91 |
| Valproate | 2.97 | 0.007 | 1.34 | 6.58 |
| Sex (Males high) | 1.90 | <0.001 | 1.43 | 2.53 |
| Age | 1.09 | <0.001 | 1.06 | 1.13 |
| RACF[1] vs Community | 1.39 | 0.022 | 1.05 | 1.85 |
| Mixed[2] (high) vs Community | 0.58 | 0.017 | 0.37 | 0.91 |
| Antidepressants | 0.72 | 0.014 | 0.56 | 0.94 |
| Anti-Parkinson's | 1.65 | 0.021 | 1.08 | 2.51 |
| Renin-angiotensives | 0.71 | 0.014 | 0.54 | 0.93 |
| Morphine use | 4.10 | <0.001 | 2.97 | 5.66 |

[1]Residential Aged Care Facility
[2]Dispensing partly in the community and partly in RACF

## 3.3 INCIDENT ANTIPSYCHOTIC, CARBAMAZEPINE AND VALPROATE SUBJECTS WITH CHOLINESTERASE INHIBITOR USE AT SOME POINT IN 2001 THROUGH 2004

In 2003 and 2004 there were 2224 incident antipsychotic, carbamazepine and valproate subjects among the DVA entitled beneficiaries 65 years and older who had been dispensed a cholinesterase inhibitor on the Repatriation Pharmaceutical Benefits Scheme (RPBS). Fifty-nine percent of subjects were male. Whilst only 12% resided in an Aged Care Facility on 1st January, 2003, 66% were resident in an Aged Care Facility at some point in 2003 or 2004. Seventeen percent of the sample had died by 31.12.04. The age distribution of the subjects is given in Table 1.

*Table 1. Age distribution at 1.1.03. of incident antipsychotic, carbamazepine and valproate subjects, also dispensed a cholinesterase inhibitor, 2001-2004*

| Age in years at 2003 | N | % |
|---|---|---|
| 65-69 | 18 | 1% |
| 70-74 | 80 | 4% |
| 75-79 | 616 | 28% |
| 80-84 | 979 | 44% |
| 85-89 | 447 | 20% |
| 90-94 | 77 | 3% |
| 95-99 | 7 | 0% |
| 100+ | 0 | 0% |

There were insufficient subjects to analyse data for three conventional AP drugs, namely chlorpromazine, haloperidol and pericyazine. The group sizes for thioridazine (N=3) and trifluoperazine (N=18) were small and they have been omitted from the following tables and analysis. There were sufficient subjects to analyse data for three atypical AP drugs, namely olanzapine, quetiapine and risperidone. There were only two subjects dispensed amisulpride and they were omitted from the following tables and analysis. Data for two anti-epileptic

drugs, carbamazepine and valproate, were also extracted. The mixed group was established as per the protocol of the general incident cohort. Those starting a second study drug were managed as per the protocol of general incident cohort. The average age, percentage male and residential status of each drug group is displayed in Table 2.

*Table 2. Incident antipsychotic, carbamazepine and valproate subjects also dispensed a cholinesterase inhibitor in 2001-2004, by age, sex and place of residence in 2003 and 2004*

| | N | Mean Age | Percentage male | Community | RACF[1] | Mixed[2] |
|---|---|---|---|---|---|---|
| **Conventional AP drug** | | | | | | |
| Chlorpromazine | 42 | 82.14 | 62% | 52% | 45% | 2% |
| Haloperidol | 732 | 82.38 | 62% | 45% | 43% | 13% |
| Pericyazine | 207 | 82.51 | 64% | 43% | 48% | 9% |
| **Atypical AP drugs** | | | | | | |
| Olanzapine | 468 | 82.09 | 54% | 41% | 45% | 14% |
| Quetiapine | 119 | 81.50 | 70% | 50% | 34% | 15% |
| Risperidone | 355 | 81.84 | 56% | 43% | 44% | 13% |
| **Others** | | | | | | |
| Carbamazepine | 84 | 81.51 | 56% | 80% | 18% | 2% |
| Valproate | 161 | 81.16 | 57% | 52% | 35% | 14% |
| Mixed | 33 | 82.34 | 67% | 15% | 76% | 9% |

[1]Residential Aged Care Facility
[2]Some dispensing occurred in the community and some in RACF

The average age for this cohort was 82.07 years. The average age of the incident cohort receiving chlorpromazine, haloperidol, pericyazine, olanzapine, quetiapine, risperidone, carbamazepine, valproate or mixed drugs was 81.70 years. Thus there was no meaningful difference in the average age of these two cohorts. Compared with the general incident cohort, this cohort had a lower percentage of subjects receiving all dispensing of the study drug in the community. This finding was present for all study drug groups. Compared with the general incident cohort, there was a higher percentage of subjects entering a residential aged care facility at some point in 2003 or 2004.

The pattern of psychotropic medication dispensing is contained in Table 3. In this cohort, compared with the general incident cohort there was higher antidepressant use in the chlorpromazine, haloperidol, carbamazepine and valproate cohorts. The mixed group had the highest level of concurrent benzodiazepine use.

*Table 3. Incident antipsychotic, carbamazepine and valproate subjects also dispensed a cholinesterase inhibitor in 2001-2004, by dispensing of other classes of psychotropic medications in 2003 and 2004*

| | Antidepressant use | Lithium use | BZDP use | Antihistamine use |
|---|---|---|---|---|
| Conventional AP drug | | | | |
| Chlorpromazine | 62% | 2% | 62% | 7% |
| Haloperidol | 52% | 0% | 61% | 13% |
| Pericyazine | 51% | 0% | 61% | 8% |
| Atypical AP drugs | | | | |
| Olanzapine | 54% | 1% | 56% | 10% |
| Quetiapine | 54% | 0% | 57% | 7% |
| Risperidone | 51% | 1% | 54% | 11% |
| Others | | | | |
| Carbamazepine | 58% | 0% | 57% | 11% |
| Valproate | 57% | 1% | 52% | 11% |
| Mixed | 45% | 0% | 73% | 6% |

The pattern for selected medical drug dispensing for the subjects is displayed in Table 4. Among the incident cohort who had been dispensed a cholinesterase inhibitor the level of diuretic use was lower, especially among the conventional antipsychotic subjects. Morphine use was lower in haloperidol subjects in this analysis compared with the general incident analysis (14% vs 28%) but higher in the mixed group (21% vs 16%). The quetiapine subjects had the lowest morphine use. Oncological drugs were less commonly used in the chlorpromazine and haloperidol groups in this analysis compared with the analysis of the general incident subjects.

*Table 4. Incident antipsychotic, carbamazepine and valproate subjects also dispensed a cholinesterase inhibitor in 2001-2004, by dispensing of selected classes of medications in 2003 and 2004*

| | Diuretic use | Glycoside use | Anti-epileptic drug use[1] | Morphine use | Coxib use | Oncological drug use |
|---|---|---|---|---|---|---|
| **Conventional AP drugs** | | | | | | |
| Chlorpromazine | 31% | 10% | 2% | 17% | 26% | 5% |
| Haloperidol | 33% | 14% | 4% | 14% | 29% | 5% |
| Pericyazine | 31% | 14% | 3% | 15% | 23% | 5% |
| **Atypical AP drugs** | | | | | | |
| Olanzapine | 31% | 12% | 3% | 10% | 25% | 4% |
| Quetiapine | 33% | 14% | 3% | 3% | 33% | 3% |
| Risperidone | 31% | 12% | 4% | 9% | 25% | 2% |
| **Others** | | | | | | |
| Carbamazepine | 44% | 19% | 12% | 10% | 35% | 6% |
| Valproate | 33% | 12% | 11% | 11% | 30% | 6% |
| Mixed | 24% | 6% | 0% | 21% | 33% | 0% |

[1]Anti-epileptic drugs excluding carbamazepine, valproate and clonazepam

The use of drugs for some movement disorders is presented in Table 5. Consistent with the findings in the other cohorts, quetiapine, and to a lesser extent olanzapine and carbamazepine subjects, were more likely to be dispensed drugs used to treat Parkinson's disease (excluding anti-cholinergic drugs) compared with other drugs groups in this cohort. Carbamazepine subjects in this cohort were more likely to be dispensed drugs used in the treatment of

Parkinson's disease compared with the general incident cohort (13% vs 4%). However, the carbamazepine group size was not large (N=84).

*Table 5. Incident antipsychotic, carbamazepine and valproate subjects also dispensed a cholinesterase inhibitor in 2001-2004, by dispensing of drugs used in movement disorders in 2003 and 2004*

| | Drugs used in Parkinson's Disease[1] | Anticholinergic drugs | Anti-cholinergic drugs without other drugs for Parkinson's Disease |
|---|---|---|---|
| **Conventional AP drugs** | | | |
| Chlorpromazine | 7% | 2% | 2% |
| Haloperidol | 7% | 2% | 2% |
| Pericyazine | 6% | 2% | 2% |
| **Atypical AP drugs** | | | |
| Olanzapine | 12% | 2% | 1% |
| Quetiapine | 24% | 3% | 0% |
| Risperidone | 7% | 0% | 0% |
| **Others** | | | |
| Carbamazepine | 13% | 1% | 1% |
| Valproate | 6% | 1% | 1% |
| Mixed | 6% | 0% | 0% |

[1]Excluding anti-cholinergic drugs

The average number of different drugs dispensed in the twelve months prior to the first date of dispensing of a study drug are displayed in Table 6. In every drug group, the mean score in this analysis was lower than the mean score for general incident subjects.

*Table 6. Incident antipsychotic, carbamazepine and valproate subjects also dispensed a cholinesterase inhibitor in 2001-2004 by average of different drug count in the year preceding first dispensing in 2003 or 2004*

| | N | Average of total number of different drugs over 12 months |
|---|---|---|
| Chlorpromazine | 42 | 11.71 |
| Haloperidol | 732 | 10.38 |
| Pericyazine | 207 | 9.46 |
| **Conventional AP drug** | | |
| **Atypical AP drugs** | | |
| Olanzapine | 468 | 10.34 |
| Quetiapine | 119 | 10.29 |
| Risperidone | 355 | 10.44 |
| **Others** | | |
| Carbamazepine | 84 | 13.07 |
| Valproate | 161 | 10.94 |
| Mixed | 33 | 8.36 |

Death per 1000 person years at risk (pyar) is displayed in Table 7. The death rate was reduced in every drug group when compared with the general incident subjects. There was strong evidence that haloperidol was associated with an increased death rate compared with pericyazine, olanzapine, quetiapine, risperidone and valproate ($p<0.05$). The small size of the chlorpromazine, carbamazepine and mixed groups was reflected in the large 95% confidence intervals. The significant difference between the death rates pyar for risperidone and quetiapine found in the general incident analysis was not replicated in this analysis.

*Table 7. Incident antipsychotic, carbamazepine and valproate subjects also dispensed a cholinesterase inhibitor in 2001-2004 by deaths per 1000 person years of exposure in 2003 or 2004*

| | N | Alive[1] | Dead[2] | Deaths per 1000 person years of exposure | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| **Conventional AP drug** | | | | | | |
| Chlorpromazine | 42 | 95% | 5% | 156 | 18 | 565 |
| Haloperidol | 732 | 86% | 14% | 324 | 264 | 394 |
| Pericyazine | 207 | 92% | 8% | 158 | 90 | 257 |
| **Atypical AP drugs** | | | | | | |
| Olanzapine | 468 | 89% | 11% | 168 | 125 | 220 |
| Quetiapine | 119 | 95% | 5% | 72 | 26 | 157 |
| Risperidone | 355 | 91% | 9% | 156 | 108 | 219 |
| **Others** | | | | | | |
| Carbamazepine | 84 | 93% | 7% | 84 | 53 | 315 |
| Valproate | 161 | 94% | 6% | 161 | 49 | 203 |
| Mixed | 33 | 82% | 18% | 282 | 103 | 614 |

[1]Subjects were considered alive if they were alive when starting a second study drug, were alive 60 days after discontinuation of a study drug, or alive at 31.12.04.
[2]Death was considered to have occurred during the drug exposure if the death occurred 60 days after the last drug dispensing.

## 3.3.1 Survival Analysis for incident antipsychotic, carbamazepine and valproate subjects who had been dispensed a cholinesterase inhibitor in 2001-2004

### 3.3.1.1Survival analysis until 31.12.04

The Relative Risk (RR) of death from initial dispensing until 31.12.04. was established using a multivariate Cox Regression. The results from the final model are displayed in Table 8. Variables with a partial p value <0.05 have been presented. Olanzapine subjects, dispensed a cholinesterase in 2001-2004, were chosen as the reference group. The relative risks are presented with respect to this olanzapine group.

*Table 8. Relative risk of (RR) death from initial dispensing until 31.12.04.in incident antipsychotic, carbamazepine and valproate subjects who had been dispensed a cholinesterase inhibitor in 2001-2004[1,2]*

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Haloperidol | 1.82 | <0.001 | 1.47 | 2.24 |
| Sex (Males high) | 1.75 | <0.001 | 1.39 | 2.21 |
| Age | 1.06 | <0.001 | 1.03 | 1.08 |
| RACF[3](high) vs Community | 1.60 | <0.001 | 1.27 | 2.02 |
| Mixed[4] (high) vs Community | 0.67 | 0.036 | 0.46 | 0.97 |
| Antidepressants | 0.70 | <0.001 | 0.57 | 0.86 |
| Anti-Parkinson's | 1.52 | 0.011 | 1.10 | 2.09 |
| Antiarrhythmics | 1.66 | 0.022 | 1.08 | 2.57 |
| Morphine use | 3.68 | <0.001 | 2.93 | 4.62 |

[1]Amisulpride, thioridazine and trifluoperazine groups not included
[2]Olanzapine subjects, dispensed a cholinesterase inhibitor, 2001-2004, were the reference group
[3]Residential Aged Care Facility
[4]Dispensing partly in the community and partly in a RACF.

Of the study drugs, only haloperidol had a significantly increased RR of death compared with olanzapine in this cohort. Whilst age, sex, residential status and morphine use remained strong predictors, drugs used in cancer and the total number of different drugs in the prior 12 months were no longer significantly associated with death. The dispensing of drugs used in Parkinson's disease and anti-arrhythmic drugs were associated with a significantly increased risk. The dispensing of antidepressant medication was associated with a reduced RR. Surprisingly, mixed residential status (some dispensing in the community and some dispensing in RACF) compared with those receiving all dispensing in the community was associated with a lower RR. The mixed group had only 271 subjects in this analysis.

**3.3.1.2 Survival analysis over 60 days**

A multivariate Cox regression ascertained the RR over 60 days for the study drugs. The resulted are presented in Table 9. Again variables with a partial p value greater or equal to 0.05 have been omitted. Olanzapine subjects dispensed a cholinesterase inhibitor in 2001-2004 were the reference group.

*Table 9. Relative risk of death over 60 days in incident antipsychotic, carbamazepine or valproate subjects who had been dispensed a cholinesterase inhibitor in 2001-2004[1,2]*

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Haloperidol | 2.59 | <0.001 | 1.79 | 3.75 |
| Age | 1.06 | 0.006 | 1.02 | 1.10 |
| Mixed[3] (high) vs Community | 0.15 | 0.001 | 0.05 | 0.47 |
| Antidepressants | 0.47 | <0.001 | 0.32 | 0.69 |
| Anti-Parkinson's | 1.84 | 0.023 | 1.09 | 3.10 |
| Morphine use | 3.91 | <0.001 | 2.64 | 5.77 |
| Total number of different drugs[4] | 1.05 | <0.001 | 1.03 | 1.08 |

[1]Amisulpride, thioridazine and trifluoperazine groups had insufficient numbers and were omitted
[2]Olanzapine subjects dispensed a cholinesterase inhibitor 2001-2004 as the reference group
[3] Dispensing partly in the community and partly in RACF
[4]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

Again haloperidol was the only drug associated with a significantly increased RR of death. This survival analysis did not find that male gender or residence in an aged care facility compared with living in the community were associated with a significantly increased RR. Mixed residential status was again associated with a lower RR of death. In the general incident subject analysis, the dispensing of drugs used in Parkinson's disease was not associated with a significantly increased RR. Indeed, in the 60 day Cox Regression in the general incident analysis the associated RR for the dispensing of drugs used in Parkinson's disease (excluding anti-cholinergic drugs) was 0.86 (95% CI 0.76-0.98).

### 3.3.2 Case Control Analysis in incident subjects who had been dispensed a cholinesterase inhibitor in 2001-2004

The results from the logistic regression comparing exposure to drugs over a sixty day study period are displayed in Table 10. The sixty day study period was either the sixty days prior to death or sixty days prior to a randomised study date. Olanzapine is not used as a reference group in this analysis. The reference group was formed by those not dispensed a study drug in the 60 day period. Amisulpride, chlorpromazine, thioridazine, trifluoperazine and carbamazepine had insufficient numbers for analysis. Thus the analysis was performed on 2179 subjects. There were insufficient subjects for lithium to be used as a covariate.

*Table 10. Odds Ratios of death from the case control study of drug exposure 60 days prior to date of death or a randomised study date in incident antipsychotic, carbamazepine or valproate users who had been dispensed a cholinesterase inhibitor in 2001-2004*[1]

| Predictor | OR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Haloperidol | 9.04 | <0.001 | 6.40 | 12.75 |
| Olanzapine | 3.85 | <0.001 | 2.61 | 5.69 |
| Pericyazine | 3.65 | <0.001 | 1.87 | 7.12 |
| Risperidone | 4.85 | <0.001 | 2.97 | 7.91 |
| Valproate | 2.97 | 0.007 | 1.34 | 6.58 |
| Sex (Males high) | 1.90 | <0.001 | 1.43 | 2.53 |
| Age | 1.09 | <0.001 | 1.06 | 1.13 |
| RACF[2] (high) vs Community | 1.39 | 0.022 | 1.05 | 1.85 |
| Mixed[3] (high) vs Community | 0.58 | 0.017 | 0.37 | 0.91 |
| Antidepressants | 0.72 | 0.014 | 0.56 | 0.94 |
| Anti-Parkinson's | 1.65 | 0.021 | 1.08 | 2.51 |
| Renin-angiotensives | 0.71 | 0.014 | 0.54 | 0.93 |
| Morphine use | 4.10 | <0.001 | 2.97 | 5.66 |

[1]Amisulpride, chlorpromazine, thioridazine, trifluoperazine and carbamazepine had insufficient numbers for analysis.
[2]Residential Aged Care Facility
[3]Some dispensing occurred in the community and some in RACF

Haloperidol, olanzapine, pericyazine, risperidone and valproate were associated with significantly increased ORs for death. Quetiapine was not associated with an increased OR. This was the case despite the association between quetiapine dispensing and the dispensing of drugs used in Parkinson's disease, and the association of the latter with an increased OR of death. The OR for haloperidol was significant when compare with olanzapine and quetiapine ($p<0.05$). Age, male gender and residence in an aged care facility were associated with an increase in the OR. Again mixed residential status compared with those receiving dispensing entirely in the community was associated with a reduced OR. As in the Cox regression in this analysis, drugs used in Parkinson's disease (excluding anti-cholinergic drugs) and morphine use were associated with increased ORs of death.

## 3.4. INCIDENT ANTIPSYCHOTIC, CARBAMAZEPINE OR VALPROATE SUBJECTS RESIDENT IN AN AGE CARE FACILITIES AT ANY TIME IN 2003 OR 2004

In 2003 and 2004 there were 6602 incident antipsychotic, carbamazepine or valproate subjects among the DVA entitled beneficiaries 65 years and older who resided in an aged care facility at some point in 2003 or 2004. Forty-nine percent of subjects were male. Whilst 35% resided in an aged care facility on 1st January, 2003, 100% (by definition) were resident in an Aged Care Facility at some point in 2003 or 2004. Twenty-nine percent of the sample had died by 31.12.04. The age distribution of the subjects is given in Table 1.

*Table 1. Age distribution at 1.1.03. of incident antipsychotic, carbamazepine and valproate subjects resident in aged care facilities at any time in 2003 or 2004*

| Age in years at 2003 | N | Percent |
|---|---|---|
| 65-69 | 41 | 1% |
| 70-74 | 204 | 3% |
| 75-79 | 1394 | 21% |
| 80-84 | 2569 | 39% |
| 85-89 | 1705 | 26% |
| 90-94 | 590 | 9% |
| 95-99 | 84 | 1% |
| 100+ | 15 | 0% |

There were sufficient subjects to analyse data for four conventional antipsychotic drugs, namely, chlorpromazine, haloperidol, pericyazine and trifluoperazine. The thioridazine group, with only 12 subjects, was omitted from the analysis. There were sufficient subjects to analyse the data for three atypical antipsychotic drugs but the amisulpride group was small (N=17) and thus omitted from the analysis. Data for two anti-epileptic drugs, carbamazepine and valproate, were extracted. Those who were incident for any two of our study drugs simultaneously were entered into the mixed group. Incident users who started a second study drug were included in the count of the first drug and censored as alive at the point of starting the second drug. The average age, percentage male and residential status of each drug group is displayed in Table 2.

The largest drug groups were haloperidol, olanzapine, risperidone, valproate, and pericyazine, in descending order. The mean age in years was older in every drug group, except amisulpride, when compared with the general incident cohort. Apart from the thioridazine group, there was a lower percentage of men in this sample compared with the general incident cohort.

*Table 2. Incident antipsychotic, carbamazepine and valproate subjects resident in aged care facilities at any time in 2003 or 2004 by age, sex and place of residence in 2003 and 2004*

| | N | Mean Age | Percentage Male | RACF[1] | Mixed[2] |
|---|---|---|---|---|---|
| **Conventional AP drugs** | | | | | |
| Chlorpromazine | 140 | 83.77 | 58% | 96% | 4% |
| Haloperidol | 2293 | 83.95 | 52% | 85% | 15% |
| Pericyazine | 548 | 84.30 | 49% | 89% | 11% |
| Trifluoperazine | 44 | 83.11 | 39% | 82% | 18% |
| **Atypical AP drugs** | | | | | |
| Olanzapine | 1348 | 83.15 | 46% | 83% | 17% |
| Quetiapine | 189 | 82.40 | 53% | 79% | 21% |
| Risperidone | 879 | 83.46 | 47% | 86% | 14% |
| **Others** | | | | | |
| Carbamazepine | 341 | 83.04 | 40% | 91% | 9% |
| Valproate | 688 | 82.42 | 48% | 81% | 19% |
| Mixed | 103 | 82.36 | 56% | 85% | 15% |

[1]Residential Aged Care Facility
[2]Some dispensing occurred in the community and some in RACF

The pattern of psychotropic drug dispensing for the subjects is displayed in Table 3. The pattern of antidepressant use was similar in the sample compared with the general incident cohort. There was an increase in antidepressant use in the carbamazepine (45% to 61%), trifluoperazine (54% to 59%) and valproate (49% to 54%) groups. There were some increases in the percentage of subjects ever dispensed a cholinesterase inhibitor in the conventional antipsychotic groups. The dispensing of a cholinesterase inhibitor in the atypical antipsychotic groups was similar in this cohort and the general incident cohort. There was increased cholinesterase inhibitor use in the carbamazepine (3% to 5%) and valproate (6% to 11%) groups in this sample compared with the general incident cohort.

*Table 3. Incident antipsychotic, carbamazepine and valproate subjects resident in aged care facilities at any time in 2003 or 2004 by dispensing of other classes of psychotropic medications in 2003 and 2004*

| | Antidepressant use | Lithium use | BZDP use | Cholinesterase Inhibitor use | Antihistamine use |
|---|---|---|---|---|---|
| **Conventional AP drug** | | | | | |
| Chlorpromazine | 49% | 2% | 63% | 14% | 10% |
| Haloperidol | 50% | 0% | 64% | 18% | 11% |
| Pericyazine | 48% | 1% | 63% | 22% | 9% |
| Trifluoperazine | 59% | 2% | 66% | 18% | 0% |
| **Atypical AP drugs** | | | | | |
| Olanzapine | 54% | 1% | 61% | 21% | 9% |
| Quetiapine | 56% | 1% | 70% | 31% | 10% |
| Risperidone | 53% | 1% | 59% | 23% | 10% |
| **Others** | | | | | |
| Carbamazepine | 61% | 0% | 60% | 5% | 17% |
| Valproate | 54% | 1% | 60% | 11% | 11% |
| Mixed | 58% | 1% | 70% | 27% | 3% |

The pattern of selected medical drug dispensing for the subjects is displayed in Table 4. Overall, morphine use was increased in this sample compared with the general incident sample. There was a slight reduction in haloperidol subjects dispensed morphine in the nursing home sample (28% to 26%). There was a reduction in the dispensing of oncological drugs in the residential aged care sample compared with the general incident sample across all drug groups.

*Table 4. Incident antipsychotic, carbamazepine and valproate subjects resident in aged care facilities at any time in 2003 or 2004 by dispensing of selected classes of medications in 2003 and 2004*

| | Diuretic use | Glycoside use | Anti-epileptic drug use[1] | Morphine use | Coxib use | Oncological drug use |
|---|---|---|---|---|---|---|
| **Conventional AP drugs** | | | | | | |
| Chlorpromazine | 41% | 17% | 5% | 21% | 21% | 6% |
| Haloperidol | 42% | 18% | 4% | 26% | 24% | 4% |
| Pericyazine | 41% | 13% | 3% | 19% | 23% | 4% |
| Trifluoperazine | 39% | 11% | 5% | 16% | 36% | 2% |
| **Atypical AP drugs** | | | | | | |
| Olanzapine | 38% | 14% | 3% | 15% | 23% | 3% |
| Quetiapine | 37% | 17% | 4% | 8% | 29% | 4% |
| Risperidone | 40% | 15% | 4% | 16% | 23% | 3% |
| **Others** | | | | | | |
| Carbamazepine | 56% | 22% | 16% | 23% | 28% | 7% |
| Valproate | 44% | 15% | 13% | 20% | 25% | 4% |
| Mixed | 37% | 16% | 5% | 20% | 23% | 2% |

[1]Anti-epileptic drugs excluding carbamazepine, valproate and clonazepam

The use of drugs for some movement disorders is detailed in Table 5. As in the other samples quetiapine, and to some extent olanzapine subjects, were dispensed drugs used in the treatment of Parkinson's disease. There was an increase in the percentage of trifluoperazine subjects who received these drugs in this sample compared with the general incident cohort. The number of subjects in the trifluoperazine group is small (N=44).

*Table 5. Subjects resident in an aged care facility who were incident antipsychotic, carbamazepine and valproate users by dispensing of drugs used in movement disorders in 2003 and 2004*

| | Drugs for Parkinson's disease[1] | Anti-cholinergic drugs | Anti-cholinergic drugs without other drugs for Parkinson's Disease |
|---|---|---|---|
| Conventional AP drugs | | | |
| Chlorpromazine | 6% | 3% | 2% |
| Haloperidol | 6% | 2% | 1% |
| Pericyazine | 7% | 1% | 1% |
| Trifluoperazine | 11% | 2% | 2% |
| Atypical AP drugs | | | |
| Olanzapine | 11% | 2% | 1% |
| Quetiapine | 28% | 4% | 2% |
| Risperidone | 7% | 2% | 2% |
| Others | | | |
| Carbamazepine | 6% | 1% | 1% |
| Valproate | 8% | 1% | 0% |
| Mixed | 8% | 2% | 2% |

[1]Excluding anti-cholinergic drugs

The total number of different drugs in a 12 month period prior to the index dispensing of antipsychotic, carbamazepine and valproate medication was extracted for each subject and the average number for each drug group established. The results are displayed in Table 6. In this sample, compared with the general incident cohort, there was a reduction in the average number of drugs in the previous 12 months in all study drugs except carbamazepine (13.71 to 14.29).

*Table 6. Incident antipsychotic, carbamazepine and valproate subjects resident in aged care facilities at any time in 2003 or 2004 by mean of different drug count in the year preceding first dispensing in 2003 or 2004*

| | N | Average of total number of different drugs over 12 months |
|---|---|---|
| **Conventional AP drug** | | |
| Chlorpromazine | 140 | 11.12 |
| Haloperidol | 2293 | 11.03 |
| Pericyazine | 548 | 9.26 |
| Trifluoperazine | 44 | 10.18 |
| **Atypical AP drugs** | | |
| Olanzapine | 1348 | 9.90 |
| Quetiapine | 189 | 10.88 |
| Risperidone | 879 | 10.22 |
| **Others** | | |
| Carbamazepine | 341 | 14.29 |
| Valproate | 688 | 11.14 |
| Mixed | 103 | 8.84 |

The death rate per 1000 person years of exposure is presented in Table 7. The rates for haloperidol and chlorpromazine were 630 and 628 deaths per 1000 person years at risk (pyar). The death rates for haloperidol and chlorpromazine were signifcantly higher than the rate for pericyazine, olanzapine, quetiapine, risperidone, carbamazepine and valproate ($p<0.05$). The haloperidol death rate in this sample (630 deaths pyar, 95%CI, 581-681) was lower than the haloperidol rate in the general incident sample (909 deaths pyar, 95% CI, 864 –957). This cohort had higher death rates compared with the general incident cohort for the following drugs: pericyazine (219 to 244 deaths pyar), trifluoperazine (96 to 296 deaths pyar), olanzapine (246 to 291 deaths pyar), quetiapine (172 to 204 deaths pyar), risperidone (276 to 307 deaths pyar), carbamazepine (102 to 174 deaths pyar) and valproate (190 to 333 deaths pyar).

*Table 7. Incident antipsychotic, carbamazepine and valproate subjects resident in aged care facilities at any time in 2003 or 2004 by deaths per 1000 person years of exposure in 2003 or 2004*

| | Alive[1] | Dead[2] | Deaths per 1000 person years of exposure | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|
| **Conventional AP drug** | | | | | |
| Chlorpromazine | 74% | 26% | 628 | 442 | 866 |
| Haloperidol | 73% | 27% | 630 | 581 | 681 |
| Pericyazine | 87% | 13% | 244 | 191 | 306 |
| Trifluoperazine | 84% | 16% | 296 | 119 | 611 |
| **Atypical AP drugs** | | | | | |
| Olanzapine | 80% | 20% | 291 | 257 | 327 |
| Quetiapine | 85% | 15% | 204 | 136 | 295 |
| Risperidone | 83% | 17% | 307 | 260 | 360 |
| **Others** | | | | | |
| Carbamazepine | 91% | 9% | 174 | 118 | 247 |
| Valproate | 81% | 19% | 333 | 278 | 396 |
| Mixed | 73% | 27% | 387 | 257 | 559 |

[1]Subjects were considered alive if they were alive when starting a second study drug, or alive 60 days after discontinuation of a study drug or alive on 31.12.04.

[2]Death was considered during the drug exposure if death occurred up to 60 days post drug dispensing

## 3.4.1 Survival Analysis for incident antipsychotic, carbamazepine and valproate subjects resident in an aged care facility at some point in 2003 or 2004

### 3.4.1.1Survival analysis from date of initial dispensing to 31.12.04

The Relative Risk (RR) of death from initial date of dispensing until 31.12.04. was established using a multivariate Cox Regression. The thioridazine and amisulpride groups have been omitted, leaving a sample of 6573 subjects. The results from the final model are displayed in Table 8. Variables with a partial p value < 0.05 have been displayed. Olanzapine subjects resident in an aged care facility in 2003 or 2004 were chosen as the reference group.

The RR for chlorpromazine (1.75, 95% CI 1.31-2.34), haloperidol (1.67, 95% CI 150-1.84), risperidone (1.19, 95% CI 1.02-1.38), and multiple drugs group (1.42, 95% CI 1.02-1.97) were significant when compared with olanzapine subjects resident in an aged care facility in 2003 or 2004. Carbamazepine was associated with a significantly lower RR. Pericyazine, trifluoperazine and quetiapine had RR not significantly different from olanzapine. This was the only Cox Regression which found a significantly increased RR associated with the dispensing of drugs for diabetes mellitus. The dispensing of morphine remained a strong predictor of mortality.

*Table 8. Relative Risk of death from initial dispensing to 31.12.04. in incident antipsychotic, carbamazepine and valproate subjects who were resident in an aged care facility at some point in 2003 or 2004*[1,2]

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Chlorpromazine | 1.75 | <0.001 | 1.31 | 2.34 |
| Haloperidol | 1.67 | <0.001 | 1.50 | 1.84 |
| Risperidone | 1.19 | 0.025 | 1.02 | 1.38 |
| Carbamazepine | 0.58 | <0.001 | 0.45 | 0.75 |
| Multiple study drugs | 1.42 | <0.036 | 1.02 | 1.97 |
| Sex (Males high) | 1.42 | <0.001 | 1.30 | 1.56 |
| Age | 1.03 | <0.001 | 1.02 | 1.04 |
| Antidepressants | 0.76 | <0.001 | 0.69 | 0.84 |
| Cholinesterase inhibitors | 0.65 | <0.001 | 0.56 | 0.74 |
| Antiarrhythmics | 1.34 | 0.003 | 1.10 | 1.62 |
| Diabetes | 1.17 | 0.031 | 1.01 | 1.34 |
| Diuretics | 1.14 | 0.008 | 1.03 | 1.25 |
| Lipid reducers | 0.81 | 0.001 | 0.71 | 0.92 |
| Morphine use | 3.29 | <0.001 | 2.99 | 3.61 |
| Coxib use | 0.74 | <0.001 | 0.66 | 0.82 |
| Total number of different drugs[3] | 1.02 | <0.001 | 1.01 | 1.02 |

[1]Insufficient numbers in the amisulpride and thioridazine groups for analysis
[2] Olanzapine subjects resident in an aged care facility in 2003 or 2004
[3]Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

### 3.4.1.2 Survival Analysis over 60 days

Table 9 displays the results of the multivariate Cox Regression over 60 days from the initial date of dispensing. Haloperidol and chlorpromazine were the only drugs associated with a significantly increased RR.

*Table 9. Relative Risk of death over 60 days in incident antipsychotic, carbamazepine and valproate subjects who were resident in an aged care facility at some point in 2003 or 2004*[1,2]

| Predictor | RR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Chlorpromazine | 2.72 | <0.001 | 1.84 | 4.01 |
| Haloperidol | 2.17 | <0.001 | 1.86 | 2.53 |
| Carbamazepine | 0.43 | 0.001 | 0.25 | 0.72 |
| Sex (Males high) | 1.42 | <0.001 | 1.22 | 1.6462 |
| Age | 1.03 | <0.001 | 1.02 | 1.0472 |
| Antidepressants | 0.66 | <0.001 | 0.57 | 0.7700 |
| Cholinesterase Inhibitors | 0.51 | <0.001 | 0.39 | 0.6562 |
| Morphine drug use | 3.06 | <0.001 | 2.63 | 3.5570 |
| Cancer drug use | 1.40 | 0.027 | 1.04 | 1.8807 |
| Total number of different drugs[3] | 1.04 | <0.001 | 1.03 | 1.0452 |

[1]Insufficient numbers in the amisulpride and thioridazine groups for analysis
[2]Olanzapine subjects resident in an aged care facility in 2003 or 2004 as the reference group
[3] Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

## 3.4.2 Odds Ratios (ORs) of death and RR in the Case Control Analysis

The results from the logistic regression comparing exposure to drugs over a sixty day study period are displayed in Table 10. The sixty day study period was either the sixty days prior to death or sixty days prior to a randomised study date. Olanzapine is not used as a reference group in this analysis. The reference group was formed by those not taking any study drug in the study period. Amisulpride, thioridazine and trifluoperazine were excluded from the analysis as there were too few subjects in these groups.

*Table 10. Odds Ratios of death from the case control study of drug exposure 60 days prior to date of death or a randomised study date in incident antipsychotic, carbamazepine or valproate subjects resided in an Aged care Facility at some point in 2003 or 2004[1].*

| Predictor | OR | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Chlorpromazine | 8.21 | <0.001 | 4.61 | 14.60 |
| Haloperidol | 10.73 | <0.001 | 8.99 | 12.80 |
| Olanzapine | 4.23 | <0.001 | 3.49 | 5.12 |
| Pericyazine | 3.24 | <0.001 | 2.33 | 4.49 |
| Quetiapine | 3.44 | <0.001 | 2.12 | 5.58 |
| Risperidone | 5.69 | <0.001 | 4.42 | 7.33 |
| Carbamazepine | 2.60 | <0.001 | 1.61 | 4.18 |
| Valproate | 5.27 | <0.001 | 4.01 | 6.92 |
| Multiple study drugs | 9.13 | <0.001 | 5.02 | 16.60 |
| Sex (Males high) | 1.44 | <0.001 | 1.27 | 1.64 |
| Age | 1.05 | <0.001 | 1.04 | 1.06 |
| Antidepressants | 0.73 | <0.001 | 0.64 | 0.83 |
| Anti-Parkinson's | 1.25 | 0.054 | 1.00 | 1.56 |
| Cholinesterase Inhibitors | 0.62 | <0.001 | 0.52 | 0.74 |
| BZDP | 0.76 | <0.001 | 0.67 | 0.87 |
| Antiarrhythmics | 1.54 | 0.004 | 1.14 | 2.08 |
| Calcium channel blockers | 0.84 | 0.039 | 0.71 | 0.99 |
| Diuretics | 1.15 | 0.047 | 1.00 | 1.31 |
| Lipid reducers | 0.77 | 0.003 | 0.64 | 0.91 |
| Morphine use | 4.28 | <0.001 | 3.69 | 4.97 |
| Coxib use | 0.66 | <0.001 | 0.56 | 0.77 |
| Total number of different drugs[2] | 1.02 | <0.001 | 1.01 | 1.03 |

[1]Amisulpride, thioridazine and trifluoperazine excluded

[2] Total number of different drugs dispensed in the year prior to the first dispensing of a study drug

There was evidence that the OR associated with haloperidol was higher then the ORs associated with olanzapine, pericyazine, quetiapine, risperidone, carbamazepine and valproate ($p<0.05$). Male gender, sex, and total number of different drugs were predictors of death. Morphine use remained a powerful predictor of mortality.

# 4. DISCUSSION

A recent meta-analysis of 15 RCTs of atypical antipsychotic drugs in dementia established an Odds Ratio (OR) of death of 1.54 (95% CI 1.06-2.23) for these drugs compared with placebo[7]. The effect of previous warnings about atypical antipsychotic drugs in BPSD, whether explicit or implied, may have promoted the use of conventional antipsychotic drugs, carbamazepine and valproate[8,73]. There is limited information concerning risk of death with conventional antipsychotic drugs. Database reviews have explored the relative risk (RR) for atypical and conventional AP medications reporting that there was no increased risk of admission for stroke between the two groups[10,35], and that conventional medications were associated with a higher RR of death[9]. The most recent warning by the US Food and Drug Administration stated that the increased risk of death may apply to conventional antipsychotic drugs as well[6].

## 4.1 HALOPERIDOL

Haloperidol was the most commonly dispensed antipsychotic medication to DVA entitled beneficiaries 65 years and older in 2003 and 2004 (N=5853). In the general incident cohort, haloperidol was significantly associated with increased mortality rate compared with every other study drug group ($p < 0.05$).The RR for haloperidol compared with olanzapine subjects in the Cox regression until 31.12.04. was 2.26 (p value <0.001, 95% CI 2.08-2.47). In the Cox regression over 60 days from initial date of dispensing, the RR for haloperidol compared with olanzapine subjects was 2.22 (p value <0.001, 95% CI 2.04-2.42). The logistic regression analysed dispensing data in the 60 days prior to the study date, which was either the date of death or a randomly allocated date. This analysis produced an OR associated with haloperidol that was significantly higher than all the other study drug groups except the mixed group (p value <0.05). The finding of increased RR and OR associated with haloperidol dispensing was consistent across the analyses of incident and prevalent subjects.

A veteran database study found an increased death rate with haloperidol compared with atypical antipsychotic medication[28]. However, in that study the drug groups were not adjusted for age, sex or medical comorbidity[28]. In a more methodologically sophisticated study, the RR of death was higher for conventional antipsychotic drug users as compared with atypical antipsychotic drug users over several time periods[9]. However, this study used aggregated conventional data and the risks may have differed among these drugs. In the light of the present study, the increased RR detected by Wang *et al.* may pertain to haloperidol rather than other conventional antipsychotic drugs. Haloperidol has been associated with higher RR of death compared with non-antipsychotic drug users[81,82]. This may not be the most appropriate comparison group, as those prescribed antipsychotic drugs may differ from non-users in cardiovascular risk factors such as obesity, smoking and exercise.

RCTs that have included haloperidol as an active comparator have not found an increased RR of death for haloperidol compared with risperidone or olanzapine[5,17]. However, the numbers in these analyses have been small and the power of these studies may have been inadequate to detect an increased risk of death with haloperidol. In the study by De Deyn *et al.* the mean haloperidol dose was 1.2mg per day[17], which may be lower than doses used in some elderly DVA entitled beneficiaries. Haloperidol has been associated with an increased OR of admission for stroke compared with risperidone[29]. Another study did not find a significant difference in the incidence of stroke among olanzapine, risperidone and aggregated conventional AP drugs[10].

Haloperidol is used for terminal agitation and delirium, conditions that in their own right increase mortality rates[30]. The models used in the present study were adjusted to reduce

confounding errors. A validated measure of overall comorbidity was used[27], as was dispensing of drugs used in the treatment of cancer and morphine. The study drugs varied significantly across all covariates (p value <0.001), although in part it was the large cohort that enabled clinically insignificant differences to be statistically significant. Eight percent of the haloperidol group were dispensed drugs used to treat cancer and 28% were dispensed morphine. Whilst the models were adjusted for these variables, there may have been other differences between the groups for which the model was not adjusted. The degree to which confounding factors were successfully adjusted affects the confidence that can be placed in the finding that haloperidol is associated with increased risk of death.

Only perfect matches with name, date of birth and date of death were accepted into the present study in order to exclude false positive matches of deceased subjects with the National Death Index data. Perfect matches occurred in only 53% of total deaths (4485/8417). Using these matches, subjects who had cancer listed as a cause of death were excluded and a Cox regression performed on the reduced sample. The RR for haloperidol was reduced from 2.26 to 2.01 in the new model and remained highly significant (p value <0.001). If the 47% of deaths that were not matched were not different from those we obtained, the RR for haloperidol would, in all likelihood, remain significant. From the change to the RR associated with covariates, it can be deduced that cancer deaths occurred disproportionately outside aged care facilities (dispensing in residential aged care facility vs. dispensing in the community, RR 1.11 to RR 1.37). As would be predicted, the RR associated with the use of anticancer drugs was reduced when cancer deaths were excluded. Morphine use remained a powerful predictor and the associated RR was only changed from 3.63 to 3.35 when cancer deaths were excluded.

There was evidence from the survival curves that those on haloperidol oral solution or receiving short-acting parenteral injections did poorly. These methods of administration may have reflected aggression, resistance to care or physical frailty. These problems in themselves may be associated with a poorer prognosis[78]. However, it is also possible that there may be a real increase in risk of death, especially with parenteral injections. Haloperidol given parenterally achieves higher blood levels than haloperidol given orally, as the parenteral route avoids the hepatic first pass metabolism. Haloperidol has strong affinity for the $D_2$ receptor (see Appendix 3 Table 1). Oral haloperidol doses of 2-3mg were associated with a significant increase in extrapyramidal side effects compared with placebo[49]. In adult patients with schizophrenia blood levels above 12ng/ml were associated with dysphoria and poorer response[114]. Akathisia, a side effect of medication, can be mistaken for psychosis or agitation due to dementia, and lead to an inappropriate increase in drug dose.

Strength as a proxy for dose was used in this study because of the limitations of dispensing data. Daily dose cannot be calculated for those who have only one date of dispensing. In those with a two dispensings, early filling of the prescription by a carer would result in a spurious increase in daily dose. A more valid indication of daily dose is achieved when four dispensings have occurred. However, to exclude those with one or two dispensings would potentially exclude those with highest risk of adverse events. The use of strength, however, has limitations. Medication may be given as a twice daily dose or scored medication may be taken as half a tablet per day. The assumption that daily dose reflects choice of strength is not unreasonable. For example those on a daily haloperidol dose of 5mg would be unlikely to be dispensed haloperidol 0.5mg tablets.

In the incident cohort there was a significant difference in survival in those dispensed haloperidol 0.5mg compared with those dispensed haloperidol 1.5mg or 5mg preparations (p<0.001). In antipsychotic naïve subjects, doses of haloperidol of 1.5mg and 5mg per day may cause significant extra-pyramidal side effects leading to falls and swallowing

difficulties. Increased risk of death with higher antipsychotic drug doses has been found in several studies. In a previous study, higher doses were associated with increased risk of sudden cardiac death[81]. The study by Wang *et al.* also found increased RR of death for those on higher doses of conventional antipsychotic drugs[9]. Dose dependent prolongation of the QTc has been noted in isolated animal hearts for haloperidol, risperidone, sertindole, clozapine and olanzapine[101]. In a meta-analysis of RCTs, dose was not associated with increased risk of death[5], but this may be due to the lower dose of haloperidol used in most RCTs. The haloperidol dose in RCTs with elderly subjects with dementia has often been lower than haloperidol 1mg per day[52,56], with the study by Devanand *et al.* a notable exception in that it used haloperidol 2-3mg per day in one group[49].

In the prevalent cohort there was evidence of a dose effect (p value <0.001). However, in this cohort the difference in survival was between haloperidol 0.5mg and 1.5mg on the one hand and haloperidol 5mg on the other. The fact that haloperidol 1.5mg was associated with a similar outcome to haloperidol 0.5mg in the prevalent group may reflect survival bias or possibly a history of gentler titration of the dose, allowing the dopamine blockade in the nigrostriatum to be partially over come by dopamine receptor up-regulation.

The prevalent cohort data provided a useful complement to the incident group data, as well as information about longer term risk. There was a reduction in the dispensing of cancer drugs and morphine to the prevalent haloperidol group, suggesting that the use in terminal agitation may be less extensive in this cohort. As expected, the mortality rate associated with the prevalent haloperidol group was lower than in the incident group, reflecting that this was a survivor group and perhaps that the use in terminal illness was less frequent. The RCTs found evidence of increased risk in the first three months of consuming antipsychotic medication however, evidence of longer term safetyhas not been established. Wang *et al.* examined risk over 180 days and found that risk of death was highest in the first 40 days[9].

The mortality rate for the prevalent haloperidol group was 243 deaths per 1000 person years at risk (pyar) (95% CI 213 to 275). There was evidence that the death rate associated with prevalent haloperidol users was higher than the death rates for all other study drugs except risperidone and the mixed group (p<0.05). On discontinuation, the survival curve for haloperidol was similar to that for risperidone discontinuation. The RR associated with in the prevalent haloperidol group in the Cox regression until 31.12.04. was 1.38 (p value <0.001, 95% CI 1.23-1.54). This RR was significantly higher than all other study drugs except for risperidone and the mixed group. The OR associated with haloperidol in the case control analysis was significantly different compared with the ORs associated with olanzapine, quetiapine, thioridazine and trifluoperazine (p value <0.05).

In the residential aged care incident subject analysis, the death rate for haloperidol was 630 deaths per 1000 person years at risk (95% CI 581-681), higher than in the cholinesterase inhibitor or prevalent analysis. Although the mortality rates were higher in the residential aged care analysis compared with the general incident cohort for all drugs except haloperidol, the RRs of death for all drugs in the survival analysis were lower than in the general incident analysis reflecting the increase in olanzapine deaths. The RR associated with haloperidol was higher over 60 days (RR 2.17 p value <0.001, 95% CI 1.86-2.53), compared with the RR from the survival analysis to 31.12.04 (RR 1.67 p value <0.001, 95% CI 1.50-1.84). The finding of greater risk over the initial period after first dispensing was consistent with the findings of Wang *et al.* [9]. The haloperidol OR from the case control analysis was significantly higher than all other study drugs except chlorpromazine and the mixed group. Interestingly, all study drugs were associated with significantly increased ORs of death in the residential aged care sample.

In summary, there is consistent evidence that haloperidol is associated with an increased risk of death in elderly DVA entitled beneficiaries. Although the models have been adjusted for comorbid medical conditions, it is impossible to exclude confounding errors for which there had been insufficient adjustment. RCTs may perhaps provide a more accurate assessment of risk, but the numbers from these trials are small and the daily dose used in RCTs may not reflect actual prescribing choices. There is strong evidence that haloperidol 1.5mg and haloperidol 5mg tablets are associated with an increased risk of death compared with haloperidol 0.5mg tablets in the general incident cohort ($p<0.001$). In this context it seems unfortunate that the Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease study, due to report in 2006, did not include haloperidol as an active comparator[33].

## 4.2 RISPERIDONE

Risperidone was associated with an increased risk of death in several of the analyses. There was evidence that the mortality rates in the general incident cohort for risperidone and quetiapine were significantly different ($p<0.05$). In addition, risperidone was associated with an increased RR of death compared with olanzapine in the general incident, prevalent and incident residential aged care analyses. The RR for risperidone, compared with olanzapine, in the general incident cohort was 1.23 (p value 0.003, 95% CI 1.07-1.40). The RR was not altered by the exclusion of cancer-related deaths. In the residential aged care cohort, risperidone was not significantly associated with an increased RR for the analysis over 60 days. The cholinesterase inhibitor sample also did not find a significant difference between RRs associated with risperidone and olanzapine however, this analysis was much smaller (N=2224).

Whilst the meta-analysis of De Deyn *et al.* did not demonstrate a significantly increased risk of death for subjects on risperidone compared with placebo[74], the meta-analysis of 15 atypical antipsychotic RCTs by Schneider *et al.* demonstrated a combined atypical antipsychotic OR of 1.54 (95% CI 1.06-2.23)[7]. In the larger meta-analysis of Schneider *et al.* there was no evidence of significant difference in ORs of death among the atypical antipsychotic drugs (aripiprazole, olanzapine, quetiapine or risperidone). The OR for risperidone was 1.30 (95% CI 0.76-2.23) and for olanzapine was 1.91 (95% CI 0.79-4.59)[7]. A retrospective cohort study found that risperidone was associated with a significantly increased RR of death compared with haloperidol[82]. The authors hypothesised that frailer patients may have been preferentially prescribed risperidone. The present study does not support the contention that risperidone is associated with an increased risk compared with haloperidol. On the contrary, the OR for haloperidol was significantly increased compared with the risperidone OR in the general incident analysis. It is worth noting that in a recent retrospective cohort review with admission for stroke as the end point, the ORs associated with risperidone, olanzapine, quetiapine or ziprasidone were not significantly different[29].

Risperidone is an $a_1$ and $a_2$ adrenergic receptor antagonist. In vitro affinity constants are presented in Appendix 3, Table 1. Theoretically this receptor activity could be linked with orthostatic hypotension, particularly in hypovolaemic individuals. Orthostatic hypotension and subsequent watershed infarct has been a proposed explanation for the increase in CVAEs associated with risperidone [10]. In the present study, diuretic use was associated with an increased RR. It was hypothesised that diuretic use in combination with $a$ adrenergic antagonist may result in increased adverse events. Interactions between age, gender and diuretic use were established for each drug group. Diuretic use was not associated with a significant increase in RR across any risperidone comparison groups. Despite the in vitro affinities of risperidone, Mintzer *et al.* reported there was no statistically significant increase

in clinically significant orthostatic hypotension between risperidone and placebo[20]. The relationship between CVAEs and orthostatic hypotension in risperidone treated subjects was reported as inconsistent by De Deyn *et al.*[74].

The comparison between risperidone and olanzapine subjects is perhaps the most appropriate. Both drugs have indications for use in schizophrenia and related psychoses. Whilst risperidone alone had the indication for treatment of behavioural disorders in dementia, and there has been widespread off-label prescribing of olanzapine for this indication[8]. Neither drug had the indication for use in delirium, although again there may be off-label prescribing supported by a few case studies and preliminary RCTs[31]. There was no evidence in this study that risperidone was more frequently used in palliative care compared with olanzapine. The frequency of drugs used in cancer and morphine dispensing was identical for both drug groups. In addition the risperidone RR in the general incident cohort was not affected by the exclusion of cancer deaths (RR 1.23 to 1.23). Drugs that have similar indications for use limit the potential confounding errors[32].

## 4.3 OTHER DRUGS

Quetiapine subjects differed from other atypical antipsychotic subjects with regard to residential status during dispensing, and increased dispensing of cholinesterase inhibitors and anti-Parkinsonian drugs. Whilst these particular differences have been adjusted, the group may possess other dissimilar characteristics that have not been adjusted. Thus the significant difference between the death rate associated with risperidone and quetiapine in the incident analysis ($p<0.05$) should be viewed with caution. The report from the CATIE study should clarify any differential risk among risperidone, olanzapine and quetiapine, at least in populations similar to the study population.

Chlorpromazine is used in palliative care as it has antiemetic properties[115]. The strong anticholinergic activity of this drug makes it an inappropriate choice in the treatment of delirium outside the palliative care setting. The death rates associated with this drug varied across the analyses. In the general incident group the death rate was second only to haloperidol and in the residential aged care cohort the death rate approached that for haloperidol. In the cholinesterase inhibitor cohort the death rate was much lower, however, there were only 42 subjects in the group. The relatively low death rate in the prevalent group, 79 deaths per 1000 pyar (95% CI 52-115), supports the contention that chlorpromazine itself may not be any more harmful than other antipsychotic medications but that the death rate is affected by confounding medical illnesses. In the incident chlorpromazine group, 18/33 subjects dispensed chlorpromazine syrup died, disproportionately contributing to the overall chlorpromazine death rate.

Thioridazine and trifluoperazine subjects differ from the pericyazine, olanzapine, risperidone and quetiapine subjects in a number of ways. They were more likely to receive all dispensing in the community and less likely to be dispensed a cholinesterase inhibitor or morphine. Triflouperazine was associated with the highest use of anticholinergic drug dispensing in the absence of dispensing for other drugs used in Parkinson's disease (5% in the incident group and 11% in the prevalent group). Neither of these drugs were noted to be associated with an increased RR of death. Thioridazine and trifluoperazine have not been promoted as drugs to treat BPSD in recent years, although there were trials assessing the use of thioridazine in dementia prior to 1989[47]. Concerns regarding prolongation of the QTc interval with thioridazine use[100], have led regulators to restrict its approved indication to treatment resistant schizophrenia.

Pericyazine, olanzapine and risperidone had similar levels of dispensing entirely in the community (44%, 44% and 39%, respectively in the incident sample). In addition they had similar use of cholinesterase inhibitors (21%, 20% and 24% respectively in the incident sample and 11%, 14% and 15% respectively in the prevalent sample). The use of morphine varied slightly (15%, 11% and 11% respectively in the incident sample and 20%, 16% and 18% in the prevalent sample). Olanzapine was more likely to be dispensed to those also dispensed drugs used in Parkinson's disease (excluding anticholinergic drugs).

Pericyazine was the fourth most commonly dispensed antipsychotic drug. The death rate associated with incident and prevalent pericyazine subjects was not significantly different from the death rates for the atypical antipsychotic medications in these cohorts. Again there was no significant difference in the death rates between pericyazine and any atypical antipsychotic medication in the residential aged care facility or cholinesterase inhibitor cohorts. Among the conventional medications pericyazine was associated with a significantly lower death rate than haloperidol and a significantly higher rate than trifluoperazine. Pericyazine subjects did not differ signifcantly from olanzapine subjects in RR of death in any analysis. The authors are not aware of any studies since 1976 examining pericyazine use in palliative care or delirium.

Carbamazepine and valproate are alternatives to antipsychotic drugs in the pharmacological treatment of BPSD, although the evidence for efficacy is best considered preliminary[23-26]. Despite limited evidence of efficacy, valproate and carbamazepine were suggested as alternate treatments for BPSD in the light of concern regarding risperidone and olanzapine[22]. They are not approved for the treatment of BPSD and have approved indications outside this diagnosis. Carbamazepine is indicated for use in epilepsy, neuralgia, mania and prophylaxis in bipolar disorders. Valproate has indications for use in epilepsy and mania, and is also used in treatment of migraine.

No other retrospective cohort study examining antipsychotic dispensing has included carbamazepine and valproate as a part of their analysis. By defining carbamazepine and valproate as study drugs, we were able to review the impact of antipsychotic drugs on mortality without any confounding effects of carbamazepine or valproate treatment. However, there were two costs associated with this approach. First, some incident antipsychotic subjects were classified as prevalent users because they had been exposed to carbamazepine and valproate. Secondly, by widening the number of study drugs, more subjects were deemed to have started a second drug and hence were censored as alive, thus reducing the absolute number of deaths in the Cox regression models.

The study design allowed the risk of death associated with carbamazepine and valproate to be compared with that for the antipsychotic drugs. In the general incident and prevalent cohorts, those dispensed carbamazepine and valproate tended to receive them entirely in the community and were less likely to have received a cholinesterase inhibitor than the atypical antipsychotic medication groups. In these cohorts, the non-dementia uses of carbamazepine and valproate may have obscured any real assessment of mortality associated with their use in BPSD. In the residential aged care cohort and the cholinesterase inhibitor cohort, dispensing to treat BPSD would have been more likely. In these cohorts, the death rates for carbamazepine and valproate were not significantly different than pericyazine or the atypical antipsychotic drugs. Whilst the RR for valproate was not significantly different from olanzapine, the carbamazepine was associated with a significantly reduced RR of death in the residential aged care sample. Carbamazepine was associated with a significantly better survival rate than valproate in the general incident and prevalent cohorts (Log Rank test $p<0.001$) but this may reflect different underlying diagnoses rather than a direct drug effect.

## 4.4 SELECTED SIGNIFICANT COVARIATES

Antidepressants and lithium were associated with lower RR, which may represent a lower mortality rate associated with a mood disorder. In a community study, antidepressants were more likely to be prescribed to those with moderate dementia than to those with mild or severe dementia[45]. A two year study with community subjects with dementia found that depression became less frequent over the period of follow-up[40].Thus the protective effect of antidepressants seen in this study may reflect their reduced use in severe dementia.

In a recent analysis with admission for stroke as an end point, dispensing of benzodiazepines was associated with a significantly increased OR compared with risperidone[29]. Our analysis only coded benzodiazepine dispensing as present or absent over the two year period, so a survival analysis would not be possible with the present data. The RR for benzodiazepines as a covariate was not associated with a significantly increased RR in the Cox regression and was associated with a reduced OR in the logistic regression analyses. There was a high degree of coadministration of benzodiazepines with antipsychotic medication in the present study, with 57-64% of antipsychotic subjects also being dispensed a benzodiazepine in 2003 or 2004. Thus the study by Finkel *et al.* would have excluded a large proportion of its potential cohort. They also would have censored any antipsychotic subjects commencing a benzodiazepine and hence bias their sample against those with more extreme agitation. The study by Finkel *et al.* awaits replication.

Dispensing of cholinesterase inhibitors was generally associated with a reduction in RR. Cholinesterase inhibitors are currently indicated for treatment of cognitive impairment in mild to moderate Alzheimer's disease. Thus, subjects dispensed these drugs may be at an earlier stage in dementia than those not receiving these drugs. The reduced RR associated with cholinesterase inhibitor dispensing may reflect different prognoses among those with vascular dementia, dementia with Lewy bodies and fronto-temporal dementia compared with those with Alzheimer's disease.

In the cholinesterase inhibitor cohort the death rates for chlorpromazine (156 deaths per 1000 pyar), pericyazine (158 deaths per 1000 pyar), olanzapine (168 deaths per 1000 pyar), risperidone (156 deaths per 1000 pyar) and valproate (161 deaths per 1000 pyar) were similar. The difference in mortality rate for quetiapine compared with these drugs failed to reach statistical significance (72 deaths per 1000 pyar, 95% CI 26-157). The only death rate significantly different from other groups was the death rate for haloperidol (324 deaths per 1000 pyar 95% CI 264-394), and only haloperidol was associated with a significant RR in this cohort. The case control analysis demonstrated significantly increased OR for haloperidol, olanzapine, pericyazine, risperidone and valproate. Only quetiapine, of drugs with sufficient data to analyse, was not associated with a significantly increased OR. These results favouring quetiapine have not been reported in other studies. In the meta-analysis of Schneider *et al.* the OR of death for three quetiapine RCTs was 1.67 (95% CI 0.70-4.03)[7].

Morphine use was the most powerful covariate predictor of death. This is unsurprising as morphine is used in terminal illnesses. This finding persists in the cholinesterase sample (morphine RR 3.68 95% CI 2.93-4.62) and residential aged care cohort (RR 3.29 95% CI 2.99 –3.61). There was a only a slight reduction in the RR for morphine when the cancer deaths were excluded, suggesting that morphine was used in non-cancerous terminal illnesses. Morphine has been used to treat BPSD although the evidence for efficacy rests only on case studies [116](abstract only reviewed).

Selective inhibitors of cyclo-oxygenase 2 (COX-2) non-steroidal anti-inflammatory drugs, rofecoxib and celecoxib, have been withdrawn from production after they were associated with acute myocardial infarction and fatal coronary heart disease in high doses[112]. In the present study these drugs were associated with a significantly reduced RR in most analyses. The dose and continuity of dispensing of rofecoxib and celecoxib were not assessed. There may be confounding variables such as severity of dementia or presence of a terminal illness which may be associated with a reduction in dispensing of rofecoxib and celecoxib.

Among the covariates associated with an increased RR, the increased RR associated with morphine use, total number of different drugs and residence in an aged care facility were understandable on the basis of medical comorbidity. The exploration of differences in study drug associated RR in subjects residing in an aged care facility was assessed in a sub-analysis. Interactions for age, gender and diuretic use were explored to assess whether the risk were evenly spread among the study drugs or pertained predominantly to selected drugs. Male gender had been associated with increased risk in a previous report of elderly DVA entitled beneficiaries[117]. It had been hypothesised that male gender may have been associated with increased vascular risk factors or higher doses of antipsychotic medication. Olanzapine had been associated with an increased mortality rate in those over 80 years[5].

Diuretic use was associated with a RR of 1.23 (p value <0.001, 95% CI 1.15-1.32). Diuretic use was one of nine classes of cardiovascular drugs that were analysed. Apart from glycosides in some analyses, these other cardiovascular drugs were not associated with increased RR of death. Whilst diuretic drug use indicates cardiovascular disease, it can also result in reduced intravascular volume and low serum potassium. Low serum potassium may predispose individuals to cardiac arrhythmias. In our analysis potassium sparing diuretics were not separated from other diuretics.

The results from the interactions do not support the hypothesis of an interaction between drugs with $\alpha$ adrenergic antagonism and diuretic use. There was no evidence of a different risk for risperidone subjects who used diuretics compared with those who did not. Haloperidol, with little affinity for the $\alpha_1$ or $\alpha_2$ adrenergic receptors, had significant differences for diuretic users versus non-diuretic users in older males (RR 1.18 two-tailed p value 0.026), younger male (RR 1.19 two-tailed p value 0.040) and younger female groups (RR 1.46 two-tailed p value 0.004). In older, pericyazine subjects, there was evidence of real difference in RR between older pericyazine subjects who used diuretics and those who did not use (male RR 1.86 two-tailed p value 0.004 and female RR 2.22 two-tailed p value 0.006). Among carbamazepine users, the use of diuretic drugs significantly reduced the protective effect of carbamazepine. Thus the data do not support an interaction between $\alpha$ adrenergic blocking drugs, such as risperidone, and diuretics. The diuretic group would need to be separated into potassium sparing and other diuretic drugs to test the second hypothesis.

Male gender was associated with increased RR in the general incident cohort (RR 1.55, p value <0.001, 95% CI, 1.45-1.66). Gender was associated with a significantly increased RR in the haloperidol, olanzapine and risperidone groups. Males may have received a higher dose due to concerns about aggression or agitation. Pericyazine and quetiapine were not associated with a significant gender effects. Both these medications were predominantly dispensed in the lowest possible strengths, to 93% and 79% of subjects respectively. There was evidence of more variation in strength for haloperidol and olanzapine subjects, who were dispensed the lowest strength in only 58% and 42% of cases respectively. Risperidone, however, was predominantly dispensed in the risperidone 1mg tablet, with 85% of subjects receiving only this strength. The variability in strengths dispensed does not, of course, prove that the higher strengths were preferentially dispensed to men. Male subjects may have had more cardiovascular risk factors. It could be that other cardiovascular risk factors which were not

measured, such as smoking or obesity, were disproportionately present in male subjects. Antipsychotic drugs may have been disproportionately dispensed to women for mood disorders, with these diagnoses carrying a better prognosis. The prevalence of major depression in women was four times that of men in a large community sample of those 65 years and older[34]. However, in the present study adjustment was made for antidepressant use, which may compensate for these difference in the prevalence of mood disorders.

Age was a significant factor in olanzapine diuretic subjects (male RR 1.52 two-tailed p value 0.028 and female RR 2.07 two-tailed p value 0.008) and in one out of four risperidone and quetiapine groups. This supports the findings of Cavazzoni *et al.* 2004 that age was a mortality risk factor for olanzapine subjects [5]. In exploring the interactions among age, gender, diuretic use and study drug, age was only stratified into two groups around the median age.

## 4.5 METHODOLOGICAL CONSIDERATIONS

The second most commonly dispensed antipsychotic medication, namely olanzapine, was chosen as the reference drug for the Cox regression. Haloperidol was more frequently dispensed but its broader clinical use makes comparison with other antipsychotic drugs less straightforward. Other analysis used aggregated data, for example conventional versus atypical drugs in the survival analysis[9]. Finkel *et al.* chose risperidone for their reference drug group[29].

The methodology for retrospective cohort reviews has been recently refined and incident user designs are thought to overcome some of the limitations of prevalent user designs. Observational studies had been reporting benefit from hormone replacement therapy in preventing coronary heart disease. The value of observational cohort studies was questioned when prospective randomised trials failed to demonstrate this benefit (cited in [109]). Early antipsychotic drug cohort studies used prevalent subjects[81,82] however, more recent studies have featured incident user designs[9,10,29,35].

Ray outlined three biases that may affect observational studies: healthy user effect, survival bias and the effect of study drugs on disease risk factors[109]. The healthy user effect is more relevant for preventative treatments, but the corollary may be true in antipsychotic user studies. Doctors and carers may choose certain medications in frailer patients, thus creating a spurious association with risk. Survival bias may have affected previous cohort studies with prevalent antipsychotic drug users[81,82]. The risk with antipsychotic drugs, as demonstrated by RCTs, was evident in the first three months. Until risk over the longer term is quantified, incident user designs eliminate a falsely low risk being estimated. Ray argued that drug treatment may influence risk factors, making it difficult to know whether to control for certain features in prevalent users. He suggested that all covariates be measured just prior to the time of first dispensing. In our study covariates were measured during 2003 and 2004. For some conditions such as cancer or epilepsy, this concern is not logical. There is no evidence that antipsychotic medication causes cancer, for example. However, there is a potential criticism that dispensing for cardiovascular and diabetic drugs should have occurred in the year prior to the first dispensing of a study drug. Anticholinergic drugs, whose dispensing may be causally related to the dispensing of an antipsychotic drug, were not used as a covariates in the analysis.

RCTs provide the best evidence of risk as subjects are randomised, which reduces confounding errors, and each subject is individually assessed. However RCTs are expensive and, due to regulatory requirements, frequently short term with a focus on efficacy rather

than safety. As many RCTs are funded by pharmaceutical companies there may be publication bias. Indeed, in the meta-analysis by Schneider *et al.,* of 15 RCTs considered adequate only 6 had been published[7]. The unpublished studies did not report greater adverse events but often had failed to prove efficacy on primary outcome measures. Retrospective cohort reviews, such as the present study, are inexpensive and examine safety in those with multiple medical comorbidities, the elderly and those using medications for "off-label" diagnoses. Given the concerns about pharmaceutical companies and bias[118], it is appropriate for governments to involve themselves in surveillance of drug safety after drugs have received regulatory approval.

A validated measure, namely, the total number of different drugs used in the 12 months prior to first dispensing, was used to control for overall medical comorbidity[27]. The *c* statistic for predicting mortality obtained by using the number of distinct drugs, age and gender, was 0.745. Using an adaptation of the Charlson index with hospital data, age and gender, the predictive value was only improved by 8%. The total number of different drugs in the 12 months prior to the index dispensing has been used to control for overall medical comorbidity in a number of recent studies[9,10,35].

Subjects were followed up until death, 60 days after discontinuation of the drug, 31.12.04, or the commencement of a second study drug. On starting the second drug, the subject was censored as alive. This method was chosen to enable deaths to be attributable to only one study drug. If both drugs were continued and death occurred it would be impossible to know which, if any, drug was related to the death. If the subject changed drugs, the subject would have been a prevalent user from the point of view of the second drug. However subjects were only entered into the analysis once, so the subjects would not have been eligible for the prevalent cohort. The censoring of data at the point of starting a second drug excluded many deaths but was logically necessary to avoid measurement bias. In the case control analysis, multiple study drug users were not excluded. The dispensings for 60 days prior to the study date were analysed and the OR of death established with those not dispensed a study drug in the 60 day window serving as the reference group.

Cox regression models, with outcome variables of admission for stroke and fractured femur, were constructed from the NSW and ACT hospital service data. The methodology was analogous to the primary analysis. There were only 57 admissions for stroke and 88 admissions for fractured femur that were included in the analysis. Although there was no difference in the RR of admission for stroke among the antipsychotic, carbamazepine and valproate subjects, the small number of admissions limits confidence in this negative finding. Similarly, there were no significant differences among the antipsychotic medications regarding RR for admission with fractured femur. Again this negative finding needs to be qualified by the small number of admissions analysed. Carbamazepine and valproate were associated with significantly fewer admissions but this may have represented overall health differences in users of these drugs rather than a specific drug effect. Antipsychotic medications have previously been associated with increased falls[105].

The present study analysed data concerning DVA entitled beneficiaries 65 years and over who resided in aged care facilities and in the community. The findings of this study are only generalisable to populations similar to the elderly DVA population. When comparing the results of this study with other studies, particularly RCTs, the characteristics of the study sample need to be considered. Some meta-analyses of atypical antipsychotic drug RCTs only included subjects in aged care facilities with dementia[74], whilst others included subjects in the community as well[7]. Some observational retrospective database reviews have found lower incidence of stroke compared to that found in RCT meta-analyses. The observational studies included community-dwelling subjects who perhaps had better overall health[29].

The strengths of this review include the large number of subjects, adjustment for medical confounding variables, thorough statistical analysis, and design features measuring dispensing over time. One of the main limitations is the use of dispensing data and the assumption that tablets dispensed were consumed. This however is a limitation shared by most observational retrospective cohort studies[9,10,29,35]. Pharmaceutical data rather than hospital admissions data were used to establish medical covariates. However, the number of different drugs dispensed in the year before the index dispensing performs well as a predictor of mortality when compared with measures derived from clinical databases[27]. In RCTs the randomisation limits the likelihood of significant confounding errors. In observational studies complex design features attempt to limit confounding errors and results must be considered in the light of these methodologies. Comparing drugs with similar indications for use limits the likelihood of confounding errors[32]. Thus haloperidol, with its broader use in terminal agitation and delirium, may be associated with increased mortality because of the inherent increase in mortality associated with these conditions. Nevertheless, haloperidol was widely dispensed to elderly DVA entitled beneficiaries in 2003 and 2004 (N=5853). The evidence from this study needs to be balanced with evidence from other similar studies. Ultimately, the safety of antipsychotic drugs at various dosages can only be established beyond reasonable doubt by large RCTs. Ironically, haloperidol was considered too toxic to be included as a comparator in a large prospective, government funded trial due to report in 2006[33].

# 5. CONCLUDING COMMENTS

Is there sufficient evidence to conclude that haloperidol is more toxic than other antipsychotic drugs? Whilst there is concern that haloperidol use in delirium and terminal agitation may have caused a spuriously increased RR of death, there is consistent evidence that haloperidol is associated with increased risk across the incident and prevalent cohorts. Despite adjustment for morphine and cancer drug use, as well as partial adjustment for cancer-related deaths, the increased risk remained. The risk associated with haloperidol continued in prevalent users, albeit at a reduced level. These prevalent subjects were not likely to have terminal agitation and the persistence of increased risk in this group suggests that haloperidol may cause harm. Haloperidol, the most commonly dispensed antipsychotic drug, was the only study drug to demonstrate an increased risk with higher strengths. There were 5853 haloperidol subjects in the total sample compared with only 143 conventional (mostly haloperidol) antipsychotic subjects in the meta-analysis of Cavazzoni *et al.*[5].

Risperidone was associated with an increased RR of death compared with olanzapine in the incident, prevalent and residential aged care cohorts. The degree to which that can be taken as evidence of differential toxicity depends upon the similarity of clinical use and the degree to which this study has successfully adjusted for confounding variables. In the meta-analysis by Schneider *et al.* there was no significant difference in OR of death among aripirazole, olanzapine, quetiapine or risperidone. In the present study there was some evidence that quetiapine was associated with significantly better outcomes than risperidone and, at times, olanzapine. However, the quetiapine groups differed from other atypical antipsychotic groups. Whilst some of these differences were adjusted for in the study, there may have been other differences for which the analysis did not adjust. Quetiapine may also have been used at lower comparative doses. The Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease study, due to report in 2006 with comparators risperidone, olanzapine and quetiapine, will hopefully answer some of these questions[33].

The strengths of this study were the large number of subjects, the linking of pharmacy and residential data, the thoroughness of the statistical analysis, measures of continuity of dispensings and the measures of medical comorbidity. Nevertheless, there were limitations of the study. It primarily used pharmaceutical dispensing data. Actual consumption of the medication may or may not have occurred. Whilst measures of medical comorbidity were used, diagnostic data were not available. The potential for confounding errors needs to be weighed when assessing the results of this study.

Whilst this analysis has primarily dealt with the risk of death, there is evidence from prospective trials that there is an increased incidence of CVAEs associated with antipsychotic drug use in BPSD[4,5]. Prior to death this may lead to increased disability, carer stress and hospitalisation. In the FDA analysis death was caused by cardiac events and pneumonia, again suggesting that increased health resources would be required prior to death. This study has not assessed the costs of using antipsychotic drugs in the elderly; however, the costs may be considerably more than the price of the drugs. Therefore, given the restricted value of these drugs in BPSD, and the harm and cost associated with their use, emphasis should be placed on supporting carers and residential aged care facilities with education, environmental manipulation and evidence-based non-pharmacological interventions. On the other hand, antipsychotic drugs should be available to those with distressing symptoms who respond to these medications. However, both physician and carers need to be informed of the potential benefit and potential risk.

In conclusion, this study in elderly veterans and war widows found that haloperidol was associated with an increased risk of death compared with other antipsychotic drugs. This is

particularly important since haloperidol is dispensed to more elderly veterans and war widows than any other antipsychotic drug. There is a clear need for further studies to replicate this finding, addressing some of the limitations in an observational retrospective cohort study such as this. Ultimately, the safety of antipsychotic drugs at various dosages can only be established beyond reasonable doubt by large RCTs.

# 6. APPENDICES

## 6.1 APPENDIX NO. 1

### Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| ADAS-cog | Alzheimer's Disease Assessment Scale-cognitive subscale |
| ADAS-noncog | Alzheimer's Disease Assessment Scale-non-cognitive subscale |
| AIMS | Abnormal Involuntary Movements Scale |
| AP | Antipsychotic drug, includes conventional AP and atypical AP |
| BPRS | Brief Psychiatric Rating Scale |
| BPSD | Behavioural and psychological symptoms in dementia |
| CGI-C | Clinical Global Impression of Change |
| CGI-S | Clinical Global Impression of Severity |
| CMAI | Cohen-Mansfield Agitation Inventory |
| CVAE | Cerebrovascular adverse event |
| CVA | Cerebrovascular accident |
| DLB | Dementia with Lewy bodies |
| EPSE | Extra-pyramidal side effects |
| NPI | Neuropsychiatric Inventory |
| NPI/NH | The Neuropsychiatric Inventory –Nursing Home version |
| OR | Odds Ratio |
| RACF | Residential aged care facility |
| RCT | Randomised, controlled trial |
| RR | Relative Risk |
| TD | Tardive dyskinesia |
| VaD | Vascular dementia |

# 6.2 APPENDIX NO. 2

## Glossary of Terms

**Atypical antipsychotic medication**
Various definitions have been used in the literature:
1. an antipsychotic drug unable to produce catalepsy in laboratory animals,
2. an antipsychotic drug having no effect on prolactin levels (this is an indirect measure of D2 receptor antagonism),
3. an antipsychotic drug displaying selectivity for D2 receptors in the mesolimbic areas,
4. an antipsychotic drug with a high 5HT2:D2 receptor blocking ratio, and
5. an antipsychotic drug with greater efficacy on negative symptoms compared with conventional antipsychotic medications.

Apart from clozapine, the medications are newer than then conventional medications and more expensive.

Clozapine, risperidone, olanzapine, quetiapine, amisulpride and aripiprazole are available in Australia, although only risperidone has the indication for use in dementia.

**Akathisia**
Subjective and/or objective sense of restlessness often associated with antipsychotic medication.

**Aspiration pneumonia**
Pneumonia caused by inhaling stomach contents. May occur with sedation or when neurological conditions, for example stroke or TD, prevent adequate protection of the airways.

**Cytochrome P450 enzyme**
Series of enzymes in the liver that are important for metabolising drugs.

**Electrocardiogram**
Non-invasive investigation that reflects the hearts depolarisation and repolarisation.

**Conventional antipsychotic medication**
Older antipsychotic medication whose potency is generally related to affinity for D2 receptor binding.

Haloperidol, pericyazine, chlorpromazine, trifluoperazine, fluphenazine, pimozide and droperidol are available in Australia. Thioridazine is available with special precautions. Zuclopenthixol acetate, zuclopenthixol decanoate, flupenthixol decanoate, fluphenazine decanoate and haloperidol decanoate are available for intra-muscular injections.

**Extrapyramidal side effects**
Dystonia, tremor and akathisia. These can be disabling and are associated with falls and swallowing problems.

**QTc interval**
QT is an interval on the electrocardiogram. The QTc is the QT interval adjusted for rate. Prolongation of the QTc has been associated with ventricular arrhythmias and sudden cardiac death.

**Tardive dyskinesia**
Abnormal muscle movements which can occur de novo but most commonly occur in those who have received antipsychotic medication.

**Torsades de pointes**
A ventricular dysrhythmia associated with QTc prolongation.

# 6.3 APPENDIX NO. 3

## Types of antipsychotic medications and their side effects

### Conventional Antipsychotic Medication

The potency of older, typical antipsychotic drugs is generally related to their ability to block dopamine receptors. All antipsychotic medications can cause neuroleptic malignant syndrome, a potentially fatal condition.

**Butyrophenones**
**Haloperidol, a butyrophenone,** was the most widely prescribed antipsychotic in the elderly veteran population in 2003 and 2004. It is a potent $D_2$ receptor antagonist (blocker). Its chemical action makes it likely to produce extra-pyramidal side-effects (EPSE) such as dystonic reaction, tremor, increased muscle tone, akathisia and tardive dyskinesia (TD).

Increased tone and rigidity frequent occur in the elderly, in part because aging is associated with lower dopamine transmission. This side effect may lead to an increase in falls, and hence fractures and hospitalisation. Akathisia is a distressing subjective and objective sense of restlessness. Akathisia may be misdiagnosed as psychotic agitation leading to an inappropriate increase in medication. In the elderly it may be misdiagnosed as an exacerbation of their behavioural and psychological symptoms in dementia.

Tardive dyskinesia is thought to result from dopamine super-sensitivity after prolonged treatment with dopamine blocking drugs. It is more likely to occur in those with a mood disorder (as opposed to those with schizophrenia), in females, in the elderly those with diabetes and those who have experienced EPSE in their treatment. It is postulated that newer antipsychotic medication which are less likely to cause EPSE, may be less likely to cause TD. TD may be associated with feeding difficulties and aspiration pneumonia.

Another butyrophenone, **droperidol,** is now unavailable in the UK because of cardiac side effects (QTc prolongation).

**Phenothiazines**
The **phenothiazines** group includes chlorpromazine, thioridazine, pericyazine, fluphenazine and trifluoperazine.

**Pericyazine** is less sedating than chlorpromazine and less likely to produce EPSE than haloperidol. Its side effect profile includes some sedation, some anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation and confusion) and may produce EPSE in the elderly. It is used in the elderly particularly when the newer antipsychotic medications are not subsidised, eg on PBS for treatment of psychotic depression.

**Thioridazine** has been shown to prolong QTc interval and currently has restricted indications for its use in Australia (adult schizophrenia unresponsive or intolerant of at least two other antipsychotics at adequate duration and dosage). Side effects include pigmented retinopathy, orthostatic hypotension, QTc prolongation, jaundice, blood dyscrasias, convulsions, dry mouth, blurred vision, urinary retention, constipation and confusion.

**Chlorpromazine** is sedating with side effects of orthostatic hypotension, photosensitivity skin reactions, QTc prolongation, jaundice, blood dyscrasias, convulsions, dry mouth, blurred vision, urinary retention, constipation and confusion. It is less likely to produce EPSE than haloperidol.

**Fluphenazine** causes the same side effects as chlorpromazine, but is possibly more likely to produce EPSE. Also available as a long-acting depot, fluphenazine decanoate (Modecate).

**Trifluoperazine**, less sedating than chlorpromazine, is less likely to cause anticholinergic side effects but more likely to cause EPSE

**Thioxanthenes**
**Flupenthixol decanoate** is available as a long acting injection. It is less sedating than the alternatives and was thought to have some antidepressant properties. Side effects include CNS disturbance, EPSE and anticholinergic side effects.

**Zuclopenthixol is** available in a long-acting injectable form as an acetate or decanoate. Side effects include drowsiness, EPSE, anticholinergic effects, blood dyscrasias and hepatic damage.

**Diphenylbutylpiperidines**
**Pimozide,** is not widely prescribed. It has been associated with QTc prolongation and sudden cardiac death. Side effects include orthostatic hypotension, EPSE, anticholinergic side effects, rash and headache.

**Atypical Antipsychotics**

The term "atypical" has a variety of definitions and largely now refers to newer more expensive antipsychotics. The definitions of "atypical" have included: unable to produce catalepsy in laboratory animals, having no effect on prolactin levels (this is an indirect measure of $D_2$ receptor antagonism), selectivity for $D_2$ receptors in the mesolimbic areas, high $5HT_2$:$D_2$ receptor blocking ratio and greater efficacy on negative symptoms compared with conventional antipsychotic medications.

**Clozapine** has been available since the 1960s but causes, amongst other things, agranulocytosis (0.8%, but higher in the elderly) and seizures. It used for treatment of psychosis in Parkinson's Disease and treatment resistant schizophrenia, but has a low incidence of use in the elderly. It binds weakly to $D_1$ and $D_2$ receptors, while having affinity for $D_4$, $5HT_2$, $5HT_3$, $\alpha_1$ and $\alpha_2$ adrenergic, Ach M1 and H1 receptors. It has a low incidence of EPSE but a high incidence of sialorrhoea and anticholinergic effects, including bowel obstruction. it has also been linked to myocarditis and cardiomyopathy.

**Risperidone is** a potent 5HT:$D_2$ receptor antagonist. When used in doses <6mg per day in adults it has a low incidence of EPSE. However in the elderly, even low doses may be associated with EPSE. It causes postural hypotension because of $a_1$ adrenergic receptor blockade. It causes an increase in prolactin levels.

**Olanzapine** is a 5HT:$D_2$ receptor antagonist. It is sedating and has some anticholinergic activity, and doesn't increase prolactin levels. It causes weight gain, increase in blood sugar levels and lipid levels. It is less likely to cause EPSE than risperidone, but EPSE may still occur in the elderly.

**Quetiapine** has a low affinity for $D_1$, $D_2$ and $5HT_2$ receptors and a moderate affinity for $\alpha_1$ and $\alpha_2$ receptors. It causes sedation and postural hypotension. Efficacy data suggests that it may be less effective than other atypical medications. There were few veterans taking this medication in 2001. It is used in psychosis in Parkinson's disease.

**Amisulpride** selectively blocks presynaptic dopamine receptors, leading to an increase in dopamine in the prefrontal cortex (theoretically this may lessen negative symptoms of schizophrenia). At higher doses it blocks post-synaptic dopamine receptors but is relatively

selective for limbic rather than striatal areas. Despite this apparent selectivity it also causes EPSE in the elderly. It prolongs the QTc interval.

**Aripiprazole** is a presynaptic $D_2$ agonist and post-synaptic $D_2$ antagonist. It may cause agitation but is unlikely to cause orthostatic hypotension or anticholinergic side effects from its receptor affinity profile.

*Table 1. Affinity Constants ($k_i$, nM) for various antipsychotic drugs(cited in Moore* et al*. [119]*

| Drug | Dopamine $D_2$ | $a_1$ | $a_2$ | histamine $H_1$ |
|---|---|---|---|---|
| Haloperidol | 1±0.04 | 46±6 | 360±98 | 3630±85 |
| Olanzapine | 11±2 | 19±1 | 228±40 | 7±0.3 |
| Risperidone | 3±0.1 | 2±0.1 | 3±0.7 | 155±35 |

# 6.4 APPENDIX 4

## Post hoc interactions

*Table 1. Number of subjects alive or dead for each drug group by age, sex and diuretic use combinations*

Alive

| | Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| I/A | Chlorpromazine | Haloperidol | Olanzapine | Pericyazine | Quetiapine | Risperidone | Carbamazepine | Valproate |
| Y,N,F | 49 | 321 | 332 | 101 | 53 | 173 | 443 | 409 |
| Y,N,M | 90 | 397 | 282 | 113 | 93 | 170 | 529 | 501 |
| Y,D,F | 31 | 184 | 160 | 42 | 25 | 93 | 295 | 286 |
| Y,D,M | 46 | 294 | 155 | 69 | 30 | 86 | 325 | 306 |
| O,N,F | 33 | 402 | 304 | 125 | 40 | 175 | 207 | 207 |
| O,N,M | 61 | 479 | 273 | 154 | 39 | 193 | 269 | 288 |
| O,D,F | 22 | 314 | 214 | 87 | 25 | 129 | 229 | 204 |
| O,D,M | 41 | 383 | 185 | 94 | 31 | 120 | 241 | 223 |
| | | | | | | | | 12274 |

Dead

| | Drug | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| I/A | Chlorpromazine | Haloperidol | Olanzapine | Pericyazine | Quetiapine | Risperidone | Carbamazepine | Valproate |
| Y,N,F | 4 | 113 | 37 | 8 | 3 | 13 | 19 | 50 |
| Y,N,M | 32 | 306 | 61 | 16 | 11 | 37 | 44 | 71 |
| Y,D,F | 11 | 129 | 16 | 8 | 2 | 16 | 26 | 35 |
| Y,D,M | 16 | 259 | 44 | 14 | 6 | 20 | 55 | 63 |
| O,N,F | 8 | 208 | 72 | 19 | 6 | 44 | 9 | 40 |
| O,N,M | 30 | 380 | 109 | 36 | 17 | 76 | 40 | 59 |
| O,D,F | 12 | 203 | 68 | 32 | 3 | 42 | 34 | 43 |
| O,D,M | 25 | 367 | 75 | 54 | 10 | 64 | 54 | 72 |
| | | | | | | | | 3856 |
| | | | | | | | | 16130 |

Y= young, O=old, D=diuretic use, N=non-diuretic use, M=male, F=female

*Table 2. Relative risk of death for drug groups by age, sex and diuretic use combinations compared with olanzapine, young, female, non-diuretic using subjects.*

| | Not adjusted for covariates | | Adjusted for covariates | |
|---|---|---|---|---|
| Drug group | RR | p-value | RR | p-value |
| Chlorpromazine - Young,NonDiuretic,Female | 0.68 | 0.4685 | 0.74 | 0.5628 |
| Chlorpromazine - Young,NonDiuretic,Male | 3.09 | 0.0000 | 2.25 | 0.0008 |
| Chlorpromazine - Young,Diuretic,Female | 2.84 | 0.0024 | 1.75 | 0.1066 |
| Chlorpromazine - Young,Diuretic,Male | 2.92 | 0.0003 | 2.79 | 0.0007 |
| Chlorpromazine - Old,NonDiuretic,Female | 2.20 | 0.0437 | 2.13 | 0.0524 |
| Chlorpromazine - Old,NonDiuretic,Male | 4.09 | 0.0000 | 3.04 | 0.0000 |
| Chlorpromazine - Old,Diuretic,Female | 4.39 | 0.0000 | 2.88 | 0.0015 |
| Chlorpromazine - Old,Diuretic,Male | 5.23 | 0.0000 | 3.25 | 0.0000 |
| Haloperidol - Young,NonDiuretic,Female | 3.14 | 0.0000 | 2.52 | 0.0000 |
| Haloperidol - Young,NonDiuretic,Male | 6.60 | 0.0000 | 4.42 | 0.0000 |
| Haloperidol - Young,Diuretic,Female | 5.51 | 0.0000 | 3.69 | 0.0000 |
| Haloperidol - Young,Diuretic,Male | 7.50 | 0.0000 | 5.27 | 0.0000 |
| Haloperidol - Old,NonDiuretic,Female | 4.24 | 0.0000 | 2.96 | 0.0000 |
| Haloperidol - Old,NonDiuretic,Male | 6.25 | 0.0000 | 4.21 | 0.0000 |
| Haloperidol - Old,Diuretic,Female | 5.39 | 0.0000 | 3.30 | 0.0000 |
| Haloperidol - Old,Diuretic,Male | 7.48 | 0.0000 | 4.97 | 0.0000 |

| | | | | |
|---|---|---|---|---|
| Olanzapine - Young,NonDiuretic,Female | | | | |
| Olanzapine - Young,NonDiuretic,Male | 1.87 | 0.0027 | 1.78 | 0.0057 |
| Olanzapine - Young,Diuretic,Female | 0.89 | 0.6941 | 0.87 | 0.6373 |
| Olanzapine - Young,Diuretic,Male | 2.35 | 0.0001 | 1.74 | 0.0131 |
| Olanzapine - Old,NonDiuretic,Female | 1.85 | 0.0023 | 1.47 | 0.0575 |
| Olanzapine - Old,NonDiuretic,Male | 3.04 | 0.0000 | 2.26 | 0.0000 |
| Olanzapine - Old,Diuretic,Female | 2.35 | 0.0000 | 1.80 | 0.0042 |
| Olanzapine - Old,Diuretic,Male | 3.37 | 0.0000 | 2.66 | 0.0000 |
| Pericyazine - Young,NonDiuretic,Female | 0.69 | 0.3414 | 0.59 | 0.1792 |
| Pericyazine- Young,NonDiuretic,Male | 1.40 | 0.2649 | 1.28 | 0.4167 |
| Pericyazine - Young,Diuretic,Female | 1.66 | 0.1911 | 1.22 | 0.6075 |
| Pericyazine - Young,Diuretic,Male | 2.05 | 0.0225 | 1.73 | 0.0811 |
| Pericyazine - Old,NonDiuretic,Female | 1.34 | 0.2982 | 0.95 | 0.8645 |
| Pericyazine - Old,NonDiuretic,Male | 2.04 | 0.0023 | 1.63 | 0.0377 |
| Pericyazine - Old,Diuretic,Female | 2.99 | 0.0000 | 2.11 | 0.0020 |
| Pericyazine - Old,Diuretic,Male | 4.34 | 0.0000 | 3.02 | 0.0000 |
| Quetiapine - Young,NonDiuretic,Female | 0.61 | 0.4115 | 0.74 | 0.6165 |
| Quetiapine - Young,NonDiuretic,Male | 1.15 | 0.6908 | 1.22 | 0.5652 |
| Quetiapine- Young,Diuretic,Female | 0.73 | 0.6634 | 0.61 | 0.4945 |
| Quetiapine - Young,Diuretic,Male | 1.71 | 0.2234 | 2.08 | 0.0968 |
| Quetiapine - Old,NonDiuretic,Female | 1.38 | 0.4596 | 1.37 | 0.4790 |
| Quetiapine - Old,NonDiuretic,Male | 3.58 | 0.0000 | 3.00 | 0.0002 |
| Quetiapine - Old,Diuretic,Female | 1.02 | 0.9711 | 1.02 | 0.9734 |
| Quetiapine - Old,Diuretic,Male | 2.58 | 0.0078 | 3.12 | 0.0014 |
| Risperidone - Young,NonDiuretic,Female | 0.75 | 0.3766 | 0.75 | 0.3625 |
| Risperidone - Young,NonDiuretic,Male | 2.04 | 0.0022 | 1.92 | 0.0052 |
| Risperidone - Young,Diuretic,Female | 1.60 | 0.1158 | 1.36 | 0.3015 |
| Risperidone - Young,Diuretic,Male | 2.28 | 0.0030 | 2.08 | 0.0084 |
| Risperidone - Old,NonDiuretic,Female | 2.15 | 0.0006 | 1.68 | 0.0199 |
| Risperidone - Old,NonDiuretic,Male | 3.44 | 0.0000 | 2.84 | 0.0000 |
| Risperidone - Old,Diuretic,Female | 2.84 | 0.0000 | 2.08 | 0.0012 |
| Risperidone - Old,Diuretic,Male | 4.66 | 0.0000 | 3.28 | 0.0000 |
| Carbamazepine - Young,NonDiuretic,Female | 0.36 | 0.0003 | 0.31 | 0.0000 |
| Carbamazepine - Young,NonDiuretic,Male | 0.70 | 0.1031 | 0.57 | 0.0115 |
| Carbamazepine - Young,Diuretic,Female | 0.73 | 0.2258 | 0.59 | 0.0431 |
| Carbamazepine - Young,Diuretic,Male | 1.33 | 0.1830 | 0.97 | 0.8884 |
| Carbamazepine - Old,NonDiuretic,Female | 0.36 | 0.0057 | 0.31 | 0.0015 |
| Carbamazepine - Old,NonDiuretic,Male | 1.22 | 0.3920 | 0.97 | 0.8958 |
| Carbamazepine - Old,Diuretic,Female | 1.23 | 0.3800 | 0.87 | 0.5540 |
| Carbamazepine - Old,Diuretic,Male | 1.73 | 0.0099 | 1.27 | 0.2616 |
| Valproate - Young,NonDiuretic,Female | 1.04 | 0.8715 | 0.88 | 0.5513 |
| Valproate - Young,NonDiuretic,Male | 1.17 | 0.4377 | 1.06 | 0.7686 |
| Valproate - Young,Diuretic,Female | 1.04 | 0.8662 | 0.86 | 0.5250 |
| Valproate - Young,Diuretic,Male | 1.71 | 0.0097 | 1.26 | 0.2680 |
| Valproate - Old,NonDiuretic,Female | 1.60 | 0.0406 | 1.27 | 0.2936 |
| Valproate - Old,NonDiuretic,Male | 1.75 | 0.0077 | 1.46 | 0.0741 |
| Valproate - Old,Diuretic,Female | 1.63 | 0.0295 | 1.27 | 0.2859 |
| Valproate - Old,Diuretic,Male | 2.53 | 0.0000 | 1.62 | 0.0183 |
| | Model | Chisquare | 4330.5 | |
| | | DF | 79 | |
| | | p-value | 0.0000 | |
| | | | Increment | Chisquare |
| | | | | DF |
| | | | | p-value |

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