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Meta-analysis of the Effect of Medication on Falls in the Elderly

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Abstract: *The objective of this study was to carry out a systematic quality review and meta-analysis of all literature published in years 1981-1997 which studied the effect of drugs in the elderly and which had analyzable data on major groups of drugs. The sources of data were reports of surveys, case-control, prospective and retrospective studies, published in English. Identified studies were assessed for (i) ecological, (ii) methodological and (iii) statistical features. The drugs were classified into four main groups, namely (a) antidepressants (b) antipsychotics, (c) diuretics, and (d) hypnosedatives. Increasing risk of falls were related in order to diuretics, hypnosedatives, antidepressants and antipsychotics: the odd ratios with antipsychotics was 42% higher than with diuretics. The conclusion was that, clinically, the following classes of drugs show a significant positive relationship with falls: antipsychotics, antidepressants and hypnosedatives. The relationship with diuretics and falls is less clear; at best, it has a weak relationship with falls.*

Keywords: *Meta-analysis, Fall, Antidepressants, Antipsychotics, Diuretics, Hypnosedatives.*

Introduction

Falls are a common and major problem amongst the elderly. They can lead to fractures, dependency and even death. Some important commonly prescribed drugs have been reported to be associated with falls but results are often conflicting. This is partly due to difficulties in controlling various confounding factors and variables, as well as to differences in methodology and the complex etiology of falls. Also, it is aware that people tend to publish positive finding and it constitutes publications bias. However, the number of publications on

the topic of medications and falls is so many that we should not overlook the possible link between the two. In order to clarify the issues further, a meta-analysis was done on fourteen studies of falls (or hip fractures) and medications. Meta-analysis is a statistical technique which permits the comparison, and sometimes the combination, of numerical results from multiple studies after they have been coded for common features. The drugs were classified into four main groups, namely, antipsychotics, antidepressants, diuretics and hypnosedatives.

Method

Literature published in English between the years 1981 and 1997 was searched through Medline under the headings of falls, medication and fractures. The publications were scrutinized and reviewed before deciding whether they should be included in the meta-analysis. Studies with un-analyzable data and studies that did not classify drugs into major groups were excluded. Studies based on patients in long-term care facilities were included (with *) provided that they had controls for comparison.

Although in the large majority of cases, the most satisfactory method of forming treatment and control group is by random allocation, sometimes, it is neither ethical nor practical to have random allocation if subjects are exposed to a potentially harmful treatment. Hence observational (comparative) studies are required in this situation. The researchers do not intervene. There are two types of comparative studies where subjects have been exposed to the risk factor other than by random assignment. One type is called a cohort or follow-up study and the second type is called a case-control (or retrospective) study. The publications that are included in this meta-analysis happen to be either prospective or non-prospective (including survey and retrospective). These studies were pooled and analyzed together.

Odds ratio is a measure of risk association in case-control, cohort, or cross-sectional study. Both individual and pooled odds ratio are used in the analyses. Their formulae are given in the Appendix A. The interpretation of odds ratio itself and a brief discussion of it can also be found there. Kleinbaum et al. [11], describe ways of calculating the confidence interval of an odds ratio, both exact and approximate. The Taylor series confidence interval has been chosen because nearly all the studies being investigated are large in sample size. They also give the full account for the calculation of the exact *P*-value and the way to obtain an approximate *P*-value. The approximate method is chosen. Since the *P*-value they obtained is for the one-sided alternative hypothesis, two times of the resulting value should be used when a two-sided alternative hypothesis is considered. The explanation can be found in Appendix B. The two-sided *P*-values were calculated for all the studies except Lipsitz [12], Yip [23] and Liu [13] because their sample size is small. In the cases of small sample size, a function called fisher.test (Fisher's Exact Test for Count Data) from S-PLUS [20] has been used to calculate the two-sided *P*-values.

Meta-analysis can be used to compare results of studies where they are addressing essentially the same issue [8]. To ensure that this is the case the principal features of the various published papers were codified under the broad headings of their ecological, methodological and statistical features. In Table 1, the criteria considered under the ecological feature were the number of subjects in each study (which were all well in excess of 90) and the subject matter. In all but three cases [16, 17, 21], this was “falls”, though the exception dealt with hip fractures specifically. Also, multiple falls means subjects who had 2 or more falls in the study period. The methodological features studied were the type of study, the outcome and the method of collecting the data. The last included General Practice records. While these were quite variable, they were in fact seeking the same items from similar populations [22].

A combination of odds ratios of several studies of the same etiological problem done at different times and places can be done by the method of Mantel and Haenszel [14] (see Appendix A). The meta-analysis function from the True Epistat is used for the calculation of confidence of intervals and the random-effect model is chosen because it is now preferred by many statisticians. This model assumes that there is a population of true effect size instead of one true effect size. This will usually give a wider confidence interval but no test for heterogeneity is required [7].

Results

The results are set out in Tables 2, 3, 4 and 5 in which the symbols represent the following quantities: a_i, b_i, c_i and d_i are the numbers of exposed cases (Drug & Fall), unexposed cases (No Drug & Fall), exposed non-cases (Drug & No Fall) and unexposed non-cases (No Drug & No Fall), for study i respectively. Also, $\hat{\psi}_i$ are their corresponding estimated odds ratios.

Table 1. Coding

	Method Feature		Statistic Feature	
Study	Study	Outcome	Age ≥	Confounder
Prudham (1981) [15] N = 2357	Survey	Fall	65	No
Granek* (1987) [6] N = 368	Case-Control	Fall	65	Yes
Ray* (1987) [17] N = 6627	Case-Control	Hip Fracture	65	Yes
Blake (1988) [2] N = 1042	Survey	Fall	65	No
Sorock (1988) [19] N = 169	Prospective	Fall	61	No
Taggart (1988) [21] N = 427	Prospective	Hip Fracture	74	Yes
Campbell (1989) [3] N = 761	Prospective	Fall	70	Yes
Cumming (1991) [5] N = 1358	Retrospective	Multiple Falls	65	Yes
Lipsitz (1991) [12] N = 126	Prospective	Multiple Falls	81	Yes
Ray* (1991) [16] N = 28542	Case-Control	Hip Fracture	65	Yes
Jantti* (1993) [10] N = 301	Prospective	Fall	61	Yes
Yip* (1994) [22] N = 126	Case-Control	Fall	65	Yes
Liu (1995) [13] N = 96	Prospective	Fall	62	No
Herndon (1997) [9] N = 1149	Case-Control	Fall	65	No

In Table 2, the stated relative risk from Ray [16] is 1.6 but we obtain 1.8 as the odds ratio. Another study [3] in Table 4 states that the relative risk is 1.59 but our calculated odds ratio is 1.52. The respective calculated odds ratio for Liu [13] appear in Table 2, 4 and 5 are 8.25, 1.06 and 1.12 but their corresponding stated values are 1.6, 1.02 and 1.04. We combine women and men together in our calculation, though in the study of Campbell et al. [3], it was found that the relative risk is significant for women but not for men.

The graphical displays in Figs. 1, 2, 3 and 4 illustrate the concordance of the results, irrespective of the drug or type of study, even without the relatively large confidence intervals of the Lipsitz study and some from that of Yip and Liu. These diagrams also emphasise an important virtue of meta-analysis in that by converting outcomes to a common metric, in this case the odds ratio, comparisons not necessarily otherwise obvious, can be made at a global level.

In Table 6, we observe that the pooled estimate of ψ is greater than unity for all groups of drugs. Not surprisingly, the hypnosedatives have the greatest effect on falls and diuretics the least. The odds in favour of a fall in conjunction with the hypnosedatives drugs is 54% more than what it is for the diuretics. The risk is marginally greater for the person on hypnosedatives drugs compared with antidepressants and antipsychotics. What is an unacceptable risk is a clinical and ethical decision outside the context of this report.

Table 2. Results of antidepressants

i	Study	a_i	b_i	c_i	d_i	$\hat{\psi}_i$	Published Values		Calculated Values	
							P - value	95% C.I.	P - value	95% C.I.
1	Prudham (1981)	36	624	87	1610	1.1	N.S.		0.7480	0.72-1.59
2	Granek (1987)	37	147	16	168	2.6	0.002		0.0018	1.41-4.95
3	Ray (1987)	36	985	105	5501	1.9		1.3-2.8	0.0008	1.30-2.81
4	Blake (1988)	21	335	16	670	2.6	<0.01		0.0032	1.35-5.10
5	Ray (1991)	144	4357	433	23608	1.8		1.3-1.9	0.0000	1.49-2.18
6	Lipsitz (1991)	17	53	3	53	5.67		1.57-20.48	0.0059	1.57-20.48
7	Jantti (1993)	52	155	23	71	1.0	N.S.		0.9036	0.59-1.82
8	Yip (1994)	14	57	10	45	1.11		0.45-2.73	0.8229	0.45-2.72
9	Liu (1995)	11	48	1	36	8.25	0.02	1.24-2.06	0.0259	1.02-66.85

Table 3. Results of antipsychotics

i	Study	a_i	b_i	c_i	d_i	$\widehat{\psi}_i$	Published Values		Calculated Values	
							P - value	95% C.I.	P - value	95% C.I.
1	Prudham (1981)	73	587	122	1575	1.6	<0.001		0.0022	1.18-2.18
2	Granek (1987)	36	148	22	162	1.8	0.045		0.0455	1.01-3.18
3	Ray (1987)	123	898	358	5248	2.0		1.6-2.6	0.0000	1.62-2.49
4	Blake (1988)	19	337	23	663	1.6	N.S.		0.1226	0.87-3.03
5	Campbell (1989)	81	139	116	425	2.1			0.0000	1.52-3.01
6	Lipsitz (1991)	6	64	2	54	2.53		0.49-13.06	0.1375	0.49-13.06
7	Jantti (1993)	100	107	42	52	1.16	N.S.		0.5596	0.71-1.89
8	Yip (1994)	25	46	6	49	4.44		1.75-11.29	0.0017	1.67-11.80

Table 4. Results of hypnosedatives

i	Study	a_i	b_i	c_i	d_i	$\widehat{\psi}_i$	Published Values		Calculated Values	
							P - value	95% C.I.	P - value	95% C.I.
1	Granek (1987)	41	143	18	166	2.6	0.001		0.0011	1.45-4.81
2	Ray (1987)	67	954	212	5394	1.8		1.3-2.4	0.0000	1.35-2.37
3	Blake (1988)	71	285	97	589	1.5	<0.05		0.0157	1.08 – 2.12
4	Sorock (1988)	18	39	26	86	1.53		0.93-2.52	0.2428	0.75-3.11
5	Campbell (1989)	48	172	71	470	1.8			0.0028	1.23-2.77
6	Lipsitz (1991)	26	44	13	43	1.95		0.89-4.30	0.1211	0.89-4.30
7	Jantti (1993)	92	115	39	55	1.1	N.S.		0.6323	0.69-1.85
8	Yip (1994)	27	44	24	31	0.79		0.39-1.63	0.4663	0.39-1.62
9	Liu (1995)	15	44	9	28	1.06	0.55	0.71-1.47	1.0000	0.41-2.75

Table 5. Results of hiuretics

							Published Values		Calculated Values	
i	Study	a_i	b_i	c_i	d_i	$\widehat{\psi}_i$	P-value	95% C.I.	P-value	95% C.I.
1	Prudham (1981)	149	511	299	1398	1.4	<0.01		0.0059	1.09-1.70
2	Granek (1987)	87	97	89	95	0.96	0.83		0.8349	0.64-1.44
3	Taggart (1988)	92	190	35	110	1.52	0.05< p <0.1		0.0696	0.97-2.40
4	Blake (1988)	92	264	153	533	1.2	N.S.		0.2016	0.90-1.63
5	Cumming (1991)	56	52	413	837	2.18		1.48-3.22	0.0001	1.47-3.24
6	Jantti (1993)	73	134	37	57	0.84	N.S.		0.4948	0.51-1.39
7	Yip (1994)	32	39	25	30	0.98		0.48-2.00	0.8571	0.49-2.00
8	Liu (1995)	19	40	11	26	1.12	0.49	0.75-1.46	0.8254	0.46-2.74
9	Herndon (1997)	82	376	145	546	0.82		0.60-1.10	0.1994	0.61-1.11

Table 6. Overall odds ratios with 95% C.I.

Drug	R	95% C.I.
Antidepressants	1.76	1.33 – 2.33
Antipsychotics	1.58	1.31 – 1.91
Hypnosedatives	1.83	1.54 – 2.18
Diuretics	1.19	0.96 – 1.47

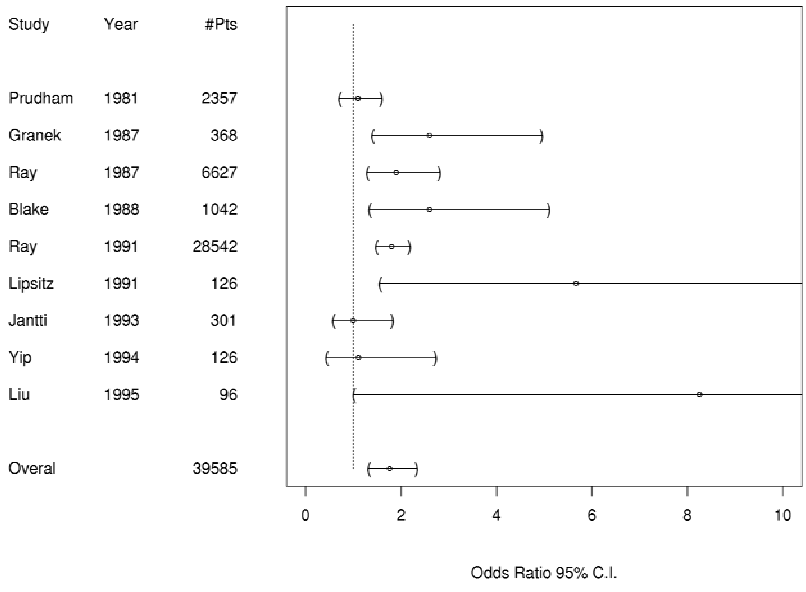

Fig. 1 Graphical result of antidepressants

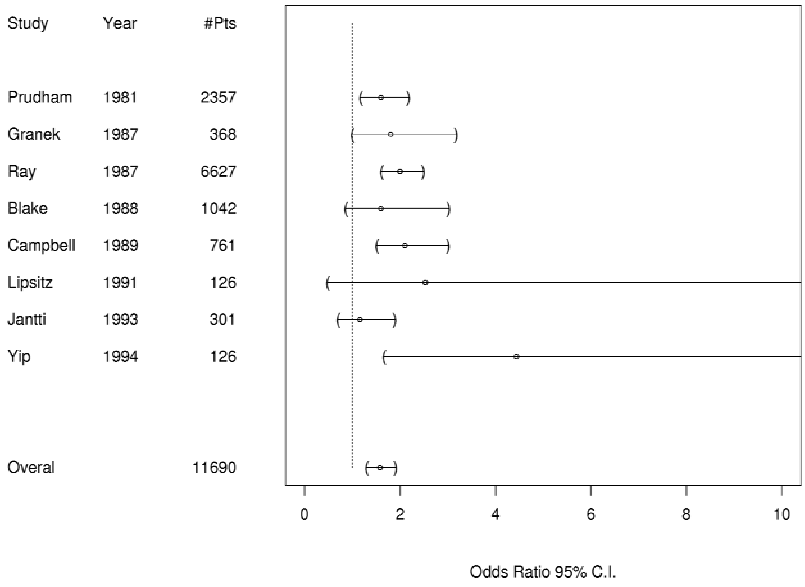

Fig. 2 Graphical results of antipsychotics

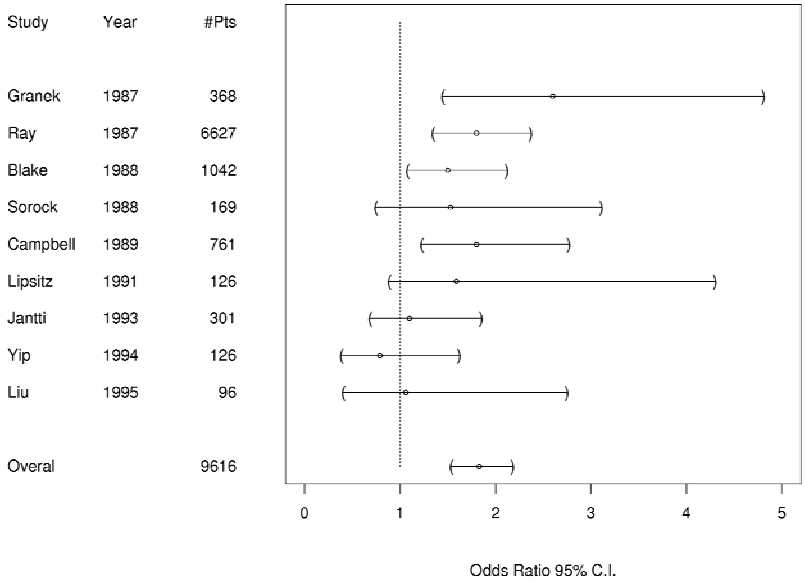

Fig. 3 Graphical result of diuretics

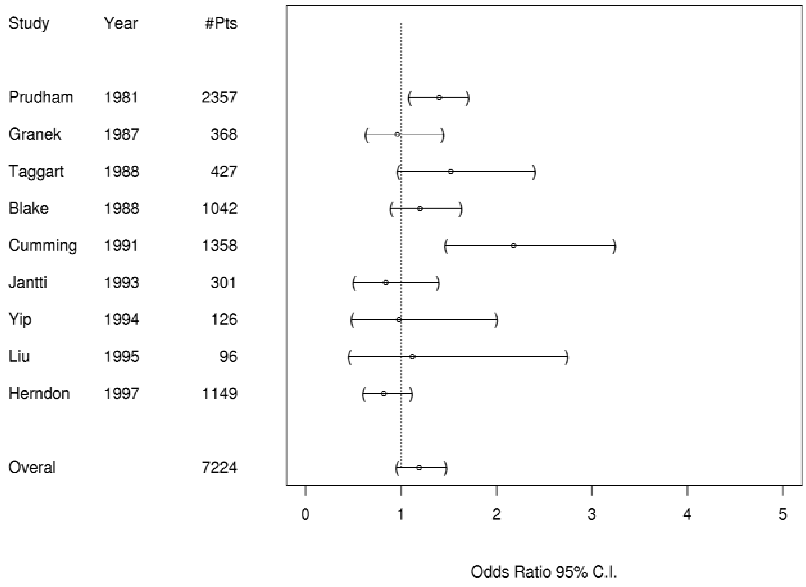

Fig. 4 Graphical result of hypnosedatives

Discusion

This meta-analysis study demonstrate that certain classes of drugs namely antipsychotics, antidepressants and hypnosedatives are associated with falls in the elderly. The overall odd ratios being 1.76 for antipsychotics, 1.58 for antidepressants and 1.83 for hyposedatives. Although it is difficult to imply a causal relationship because some of the conditions that these drugs are prescribed for may cause falls (e.g. dementia patients who are on antipsychotics or hypnosedatives), clinicians should still be vigilant about prescribing these drugs for the elderly especially when they may have underlying risks for falls. The general guidelines for prescribing medications for elderly who are prone to fall have been described previously by Chan and Gibian [4] and are summarized in the listing:

1. Avoid known offending class of drugs if possible.
2. Avoid poly-pharmacy and use the least possible dosage.
3. “As required” prescribing is preferable to continuous usage wherever possible.
4. Choose the safest drug within subgroups of drugs if usage is deemed necessary (e.g. short-acting benzodiazepines).
5. Identify the high-risk patients and always have a high index of suspicion that any drug can predispose falling
6. Warn patients of potential side effects. Monitor and review regularly, looking for side-effects.
7. Balance the risks and benefits of using a medication (e.g. L-dopa can aggravate postural hypotension but improves mobility).

There is no association between the diuretic class of drugs and fall despite the overall O.R. is 1.19 because its C.I. is 0.96-1.47 and has included the value of one. The implication of this result is worth noting since diuretics is an important class of drugs especially for treatment of cardiac failure.

One possible drawback of grouping different drugs into classes is that we are assuming all drugs in one class of drug (e.g. antipsychotic) are the same. Indeed we do not know if

different drugs classified under the same class carry equal risk for falls in the studies that we reviewed. However it is not the objective of this meta-analysis to separate them (ref. to "Method", criteria for inclusion) since we are merely interested in analyzing classes of drugs rather than any particular drug. Besides the number of studies looking into falls and any particular drug alone is far too small as identified in our Medline search.

Another possible weakness is that in the studies reviewed, 5 out of 14 studies had not controlled for confounders. Some of the other medications that the subjects were taking may influence falls via interaction or simply acting as confounder. This point reiterates the difficulty in implying a causal relationship. However, the fact that the overall odds ratios for antidepressants, antipsychotics and hypnosedatives are statistically significant cannot be undermined.

In conclusion, this study illustrates an interesting relationship between various classes of drugs and falls in the elderly and serves to remind clinicians to prescribe these drugs with care. When these drugs are required because of clinical indications, it should therefore be prescribed at the lowest effective dose and be reviewed regularly or on an as necessary basis if appropriate. Further studies into safer subclasses of drugs and safe dosages may be helpful in the reducing the risk of medications in relationship to falls in the elderly.

Appendix A

In a 2×2 contingency table of the study i, the cell entries a_i, b_i, c_i and d_i are the numbers of exposed cases, unexposed cases, exposed non-cases and unexposed non-cases, for study respectively. In this case, the odds ratio reflects the relative importance of the occurrence of a disease or an event in the presence and absence of a risk factor. It can be estimated by

$$\psi = \frac{a_i\, d_i}{b_i\, c_i}.$$

For example, an odds ratio of 2 means the odds of B are twice as high when A is present compared to when A is absent. Suppose Factor A and Factor B are an exposure factor and an outcome of an event respectively. $\psi > 1$ indicates that exposure is associated with an increased risk of developing the outcome whereas $\psi < 1$ indicates that exposure is associated with a reduced risk. It is rare to get exactly $\psi = 1$ even when exposure and outcome are not associated because there are always small increases or decreases from 1 by chance. However, the higher the value of ψ, the greater the risk of developing the outcome. As ψ gets close to zero, the exposure helps against developing the outcome.

Sinclair and Bracken [18] give a thorough discussion on odds ratio. They point out that the odds ratio calculated for favorable events is reciprocally related to that calculated for unfavorable events and this symmetry constitutes a clinically useful advantage. It can also be used as an approximation of relative risk which cannot be calculated in a case-control study. The odds ratios is a fairly good estimate of the true relative risk of exposure in the target population if the outcome is rare, i.e., $a_i << c_i$ and $b_i << d_i$. However, it is not correct to mislabel and misinterpret an odds ratio as relative risk.

The odds ratio has been used a lot by reviewers when summarizing the results of a group of trials in meta-analysis. The pooled estimate of ψ is then

$$R = \frac{\sum(a_i\, d_i / n_i)}{\sum(b_i\, c_i / n_i)}$$

where $n_i = a_i + b_i + c_i + d_i$. It is described in Armitage and Berry [1].

Appendix B

Kleinbaum et al. [11] have described how to obtain an approximate *P*-value. It should be noted that the approximate *P*-value they calculated is for the one-sided alternative hypothesis. Hence, for a two-sided alternative hypothesis, the approximate *P*-value is $2 \times pr(Z > z_i)$ where

$$z_i^2 = \frac{(n-1)(a_i\, d_i - b_i\, c_i)^2}{(a_i + c_i)(b_i + d_i)(a_i + b_i)(c_i + d_i)}$$

and Z is a standard normal variate.

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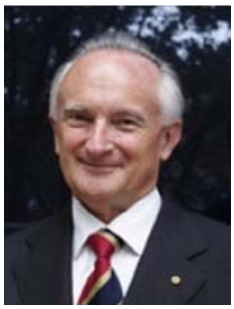

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Professor Daniel KY Chan is the director of Aged Care and Rehabilitation at Bankstown-Lidcombe Hospital and a conjoint Professor of Geriatrics within the School. He has multiple qualifications which gives him relevant background in his current roles – as a manager (MHA, AFCHSE), a staff specialist (MBBS, FRACP, FHKCP) and a enthusiastic medical researcher (MD). He is involved in undergraduate medical student teaching and a qualified Master and PhD supervisor.

Prof. Chan has broad research interests, ranging from basic science to health care service related topics. One of his main interests is finding the genetic and environmental risk factors for a number of neurodegenerative diseases such as Parkinson's disease and vascular dementia. National and international collaborations have been established for the studies of the genetic associations which includes Australia, mainland China, Hong Kong, Singapore and Japan. In addition, he has been involved with large-scale epidemiological studies, surveying over 7000 households for prevalence of Parkinson's disease and interviewing identified Parkinson's patients in Metropolitan Sydney area. Longevity and healthy ageing is another collaborative study currently in progress of recruiting and interviewing subjects who are healthy elderly aged 80 years and over.

He has also been involved with stroke service related research and stroke epidemiological research projects. His effort in establishing better stroke unit model has resulted in invitation as a keynote speaker in the International Stroke Conference in Shanghai April 2004 and invitation to present the experience and results in many other conferences in Asia Pacific area (Singapore, Hong Kong, Australia, etc). Neurologists from China and geriatricians from Singapore have come to learn from the comprehensive stroke unit model in Bankstown Hospital. He and his team won Baxter Finalist Award from NSW health department for the innovative care approach to stroke care in 2002. This year, he is involved with a comprehensive stroke care model trial funded by the NHMRC as a chief investigator. Results of most of his research projects have been published in various scientific journals with over 50 publications in peer-reviewed journals in the past five years and about two-fifth of these as first author.

Prof. Chan has been successful in securing in excess of $2 million from various competitive grants as a first applicant. Sources of grants include: NHMRC, Hong Kong Research Council; New South Wales Health Department; Australian Council for Safety and Quality in Health Care (Commonwealth); Royal Australasian College of Physicians.

Prof. Chan is the honorary professor of the institute of Geriatrics, Beijing Hospital, China, the honorary overseas editor for the "Journal of the Hong Kong Geriatrics Society", and since 2006, he is also the international advisor for the "Asian Journal of Gerontology and Geriatrics". He has been invited as keynote speakers at scientific meetings held in China, Singapore and Malaysia.

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He enjoys reading, hiking, theatre, watching soccer matches, and history.