Use of antipsychotics and benzodiazepines for dementia: Time for action? What will be required before global de-prescribing?

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TITLE: Use of antipsychotics and benzodiazepines for dementia: Time for action? What will be required before global de-prescribing?

Running Title: De-prescribing antipsychotic drugs for dementia

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Abstract:

Lessons yet to be learned when improving the treatment of Aged Care Mental Health and Dementia.

Comparing how nations including the UK, USA, Canada, Australia and others have made attempts aimed at improving the care and treatment of dementia patients can provide useful insights into methods that prove successful. The UK based 2009 Banerjee Report (Banerjee, 2009), provided international leadership in addressing treatment and practices for dementia patients with an aim to reduce prescribing of antipsychotic drugs. A historical account of the different government policies and developments with the similar aims of de-prescribing are examined. Using Australia as one example, different national strategies are discussed in the context of those that have been tried and failed. In addition, policies that have successfully reduced the controversial current practices of overprescribing antipsychotics or related psychotropic drugs for dementia patients are presented. The evidence overwhelmingly indicates such treatments only exacerbate the disease or precipitate death - giving justification to the recent call for use of chemical restraints such as antipsychotics to be included under "Elder Abuse" when considering law reform necessary to regulate compliance (Alzheimer's Australia, 2016; Banerjee, 2009).

Keywords: review, antipsychotic drugs, benzodiazepines, dementia, health care policies, de-prescribing, all-cause mortality, improving clinical compliance.

Introduction.

Dementia: A looming crisis globally and typified by Australian statistics as a case study.

Along with longer life expectancy comes a risk of dementia with upper limits in Australia showing almost 1 in 5 are diagnosed by age 70 years, increasing to 1 in 3 over age 85 and nearly 1 in 2 by age over 90 (Heuvel, Hudson, & Cargill, 2012) (Fig. 1).

Figure 1.

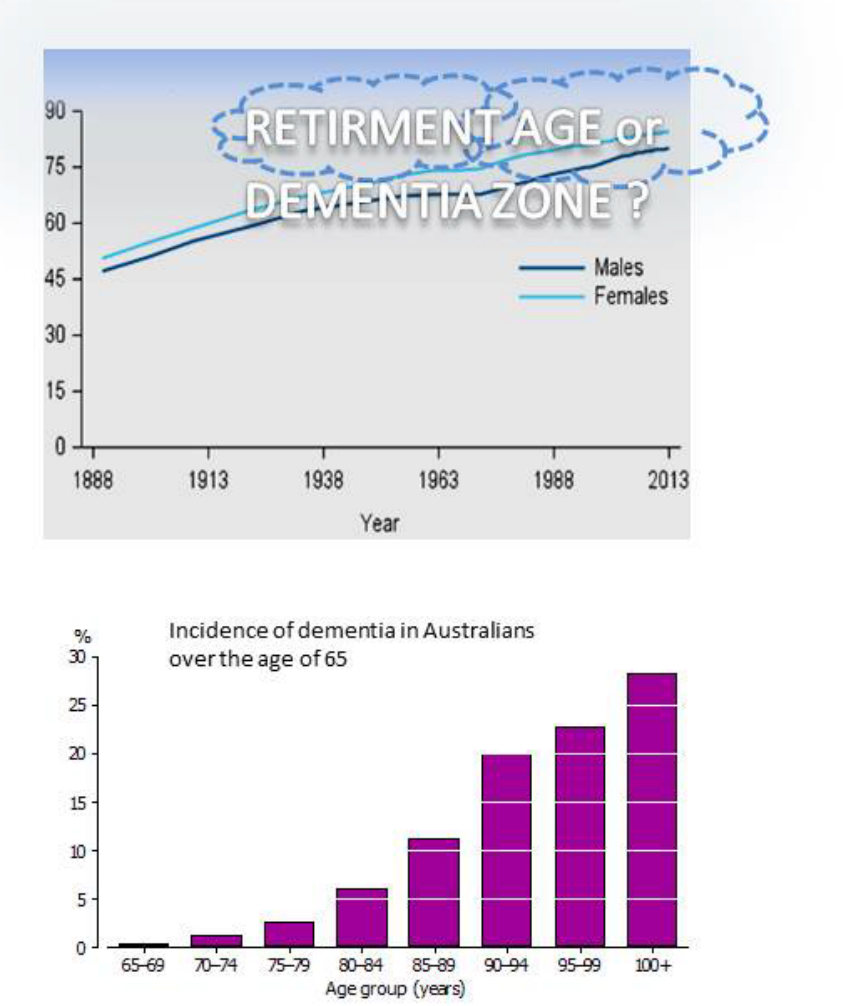

Fig. 1. Bracket creep in life expectancy pushes us into the dementia zone.

Risk of dementia onset increases significantly as people age over the retirement cut-off of 65 years old. Source: Australian Bureau of Statistics 2009 Survey of Disability, Ageing and Carers, and modified from (Australian Bureau of Statistics (ABS), 2014).

Australians are undergoing a rise in their age of retirement along with longer life expectancy – the latter currently averaging 84 years for women and 80 years for men, increasing about 2.5 years every decade (Australian Bureau of Statistics (ABS), 2014). Hence, retirement with dementia is becoming a more likely prospect for many with the proportion of deaths due to dementia and Alzheimer's disease increasing from 4.9% in 2006 to 7.9% in 2015. Dementia has become the second leading underlying cause of death (Australian Institute of Health and Welfare (AIHW), 2016b) and is predicted to become the leading cause of death within several years in Australia (Australian Bureau of Statistics, 2016).

In England and Wales, dementia has reached this status already, as the leading cause of death at 11.6% in 2015 (Office for National Statistics (ONS), 2015). Whether dementia numbers will continue to show a commensurate increase with an expanding aged population is unclear, although similar changes are happening in most industrialized nations. When considered together with the average survival data from UK and Canadian studies which show that time from dementia diagnosis until death is typically between 3 to 5 years (Meng et al., 2011; Xie, Brayne, & Matthews, 2008), a healthy retirement for many might appear as an increasingly forlorn prospect. Dementia represents a large percentage of older, mostly female patients requiring greater numbers of hospitalizations, clinical investigations, secondary diagnoses, and mortality rates commonly presenting with a prevalence of comorbidities including cerebrovascular disease, pneumonia, and hip fractures, amongst other health issues (Jackson, Schneeweiss, VanderWeele, & Blacker, 2014). Consequently, Australians living with dementia are becoming a huge health concern and current estimates indicate well over 400,000 Australian cases exist, amounting to over 50% of residents in aged care facilities, at an annual cost around AUS *$6.6 billion*

(Alzheimer's Australia, 2011). This is projected to grow to 1 million cases by 2050 costing annually over AUS *$36 billion.* This review addresses use of antipsychotics and benzodiazepines as chemical restraints for current dementia treatments under the auspices of dealing with the behavioural problems of patients. Such approaches are clearly being inappropriately used under most circumstances with unacceptable adverse effects and a big question that we are faced with is what we should and should not do to avoid a worsening medical crisis that is already affecting the retirement of an increasing number of the elderly globally.

Why are antipsychotic drugs and other psychotropics such as benzodiazepines overprescribed for dementia? The problem.

Up to 90% of people with dementia experience Behavioural and Psychological Symptoms of Dementia (BPSD), typically manifested as aggression, agitation, loss of inhibition and psychosis (delusions and/or hallucinations) (Cerejeira, Lagarto, & Mukaetova-Ladinska, 2012). These symptoms can be distressing for the person and their caregivers as well as placing the afflicted person at great risk to their health. The evidence shows that Alzheimer's patients with psychoses or agitation–aggression often respond to antipsychotic drugs or benzodiazepines as chemical restraints, reducing the severity of their behavioural problems, but may be more effectively used for particular symptoms, such as anger, aggression, and paranoid ideas (Sultzer et al., 2008). However, they do not improve functioning, care needs, or quality of life (Sultzer et al., 2008). In addition, problems can arise if antipsychotic medication is discontinued, when dementia patients may frequently relapse with their behavioural issues (D. P. Devanand et al., 2012).

From one of the earlier national reports publicized in the UK in 2009 (Banerjee, 2009), it was concluded that although antipsychotic drugs can be effective at reducing psychotic problems such as delusions, they were also linked with serious adverse effects, provided moderate benefit and failed to address the underlying causes of BPSD. In this 2009 UK Department of Health nationwide study of Banerjee (Banerjee, 2009), of the 180,000 prescriptions for people with dementia, the majority (140,000) were considered inappropriate, with prescribing antipsychotic drugs considered to be extremely harmful. Such inappropriate overprescribing of antipsychotic drugs was estimated to contribute to 1,800 deaths in the UK per year (Banerjee, 2009). Studies the same year had shown up to a 9 fold risk of stroke in the first 30 days after commencing antipsychotics in elderly patients (Kleijer et al., 2008). In a recent meta-analysis of 20 significant studies worldwide since 2009 (including several more recent large retrospective studies with more extensive longitudinal data) of over 380,000 dementia patients, the evidence overwhelmingly indicated that such drugs precipitate excessive all-cause risk of mortality, outlining the adverse impacts of antipsychotic drugs in dementia (Ralph & Espinet, 2017).

Nevertheless, more recently, in 2015, a report (Sheehan et al., 2015) from the UK showed that the number of patients at doctors' clinics with cognitive impairment also being treated with psychotropic drugs has remained far in excess of those with mental illness. The authors concluded that people without mental illness, but who had dementia (BPSD) were being given potent antipsychotic drugs which should only be approved for use in people with schizophrenia or bipolar disorder, and hence, were being used more to manage and control the behaviour of aged dementia patients (Sheehan et al., 2015). The authors added that the risks and benefits must be carefully considered before prescribing antipsychotics to

dementia patients without severe mental illness because the research evidence did not support using antipsychotics to manage their behavioural problems. Furthermore, it was concluded that many people with such dementia related behavioural disturbances have complex needs and that any medications should not be prescribed lightly and are no substitute for more comprehensive patient care.

A history of inadequate health care policies worldwide - using Australia as a case study- concerning antipsychotic medication in long-term care of aged persons with dementia – lessons learned.

In 2005, the Australian government announced the 'Dementia Initiative' (*also known as* the 'Dementia—A National Health Priority Initiative') (Department of Health, 2005). Then in 2006, at the Australian Health Ministers' Conference, it was agreed to establish the National Framework for Action on Dementia 2006–2010 (NFAD) to bring together strategies from all jurisdictions 'to treat, improve care of and delay onset or progression of dementia' (Australian Health Ministers' Conference (AHMC), 2006). In 2011, in a report prepared for the Department of Health and Ageing by the independent group, Alzheimer's Australia, an advocate organization for dementia patients was highly critical about the lack of government policy regarding the health crisis of the elderly with dementia (Alzheimer's Australia, 2012a). In March 2012, the Australian House of Representatives Standing Committee on Health and Ageing announced an inquiry into dementia calling for public submissions and this was finally published as ***"****Thinking Ahead*: Report on the inquiry into dementia: early diagnosis and intervention" (Standing Committee on Health and Ageing, 2013). Meanwhile, the 2011 report of '*Alzheimer's Australia damns dementia care'* was discussed on the Australian Broadcasting Corporation (ABC), reported on 9th April 2012

(ABC Lateline, 2012a). Following this, on 20th April 2012, then Prime Minister Julia Gillard and Minister for Mental Health and Ageing, Mark Butler announced the "Living Longer Living Better" Aged Care Legislation Act (2013), introduced to amend the previous Aged Care act of 1997. This contained a package of proposals for reform that included the House of Representatives Standing Committee on Health and Ageing inquiry into dementia. Alzheimer's Australia was the first interest group presenting at the committee with a submission from their National Office (Alzheimer's Australia, 2 May 2012) in which a major issue raised was the use of antipsychotic drugs in aged care. The following excerpts are from

> ***Poor assessment and diagnosis also leads to poor medical management (Bradford, Kunik, Schulz, Williams, & Singh, 2009).*** Evidence shows that large numbers of people with dementia are missing out on potentially beneficial symptomatic medications,(Prince, Bryce, & Ferri, 2011) are being overprescribed potentially dangerous psychotropic medications (often as a blunt means of suppressing behavioural and psychological symptoms of dementia (Banerjee, 2009)) and are at risk of unnecessary hospitalisations where they may receive invasive surgical or medical interventions

the Alzheimer's Australia report and highlight the outcomes:

5 months later on 16 Aug., 2012, a second important television program called "*Families count costs of dementia drugs prescriptions*" (ABC Lateline, 2012b) was aired nationwide simultaneously with release of a position statement from Alzheimer's Australia entitled "Antipsychotic medications and dementia" (Alzheimer's Australia, 2012b). This precipitated another major rethink by the Australian public, greatly increasing awareness including that of the Australian government's position on the plight of those in aged care facilities with mental disabilities such as dementia. The report contained the bold statement "Alzheimer's Australia believes that the potential risks of antipsychotic medications are likely to outweigh potential clinical benefits for as many as 80% of the 50-100,000 people with dementia in Australia receiving antipsychotic medications. As a result, it is likely that there are a

significant number of potentially avoidable deaths, strokes and serious side effects within this group."

The House Standing Committee report of 2013 concluded: "Unfortunately, evidence indicates that there is a lack of dementia awareness within the wider community. Misinformation about dementia has contributed to a widespread belief that dementia is an inevitable consequence of ageing, and that nothing can be done to delay onset or slow progression. Furthermore, stigma remains a significant barrier. It seems that many people are reluctant to seek an assessment when they notice signs of cognitive decline, and that doctors can be reluctant to give a diagnosis of dementia. The need for greater dementia awareness and for de-stigmatisation to increase opportunities for early diagnosis and intervention was a consistent message" (Standing Committee on Health and Ageing, 2013). In March 2014, Alzheimer's Australia released another report which indicated meanwhile that little had changed since 2012 in the use of restraints and psychotropic medications for dementia (Peisah & Skladzien, 2014), reiterating the statement that "up to 80 per cent of dementia patients in aged care facilities are being treated with psychotropic drugs". This was followed at about the same time by the release of a 112 page report from The Senate Community Affairs Secretariat, References Committee (Senate Community Affairs References Committee, 2014) entitled "Care and management of younger and older Australians living with dementia and behavioural and psychiatric symptoms of dementia (BPSD)". The following excerpt is taken from this report: ***INSERT TEXT BOX "Chemical Restraints" HERE***

Chemical Restraints or Chemical Sedation ?

"Unfortunately, the committee also heard allegations that restraints were used for the convenience and protection of the facility, rather than the clinical needs of the patient."

6.8 The evidence received by the committee points to a troubling trend in which there is an increased use of restraints as a management tool for BPSD, often used in the absence of guidelines about their appropriate use and management. The committee heard that: "…anecdotally we are getting and seeing increasing reports of the use of restraints, particularly chemical restraints in aged-care settings. That is and of itself, particularly the use of antipsychotic medications, is of particular concern to me."

6.9 Alzheimer's Australia estimated that only one-in-five dementia sufferers currently on antipsychotics currently need to be on them.

6.10 The committee heard that the over prescription of antipsychotic medication can present more risks to the health of a person than the behaviour that the medication was introduced to control. As one witness related: She was at risk of falls, because of the over-medication; she was drowsy and really unable to do any of the personal care and so forth, so required a lot more support from us…Sometimes medication that is over-prescribed can have a huge detrimental effect on the person and create more concerns for that person than they would if they had the behaviour.

6.11 Morbidities that may come with these medications include cardiac deaths, strokes, falls and other injuries. The committee also heard of cases where patients were given combinations of medication to control behaviours resulting in hospitalisations as a consequence of adverse reactions to those medications.

6.25 Evidence received from the Department appears to confirm the suspicions of a number of submitters to this inquiry: that the use of drugs in dementia is higher than would be expected on clinical grounds alone. The committee heard: The drug utilisation subcommittee has become concerned about the use of antipsychotic medication in comparison with the prevalence of depression or schizophrenia at the population level. They undertook a comparison at the end of last year and at the beginning of this year. The reports show that the use of PBS-listed antipsychotics is growing at a higher than expected rate. It is growing at a higher rate in the elderly. In February 2013 the Pharmaceutical Benefits Division was noted to have identified that there was a high and inappropriate utilisation of antipsychotics in the elderly, especially in the case of two drugs: quetiapine and olanzapine, which were prescribed at a rate entirely inconsistent with the age-specific prevalence of bipolar disease or schizophrenia in Australia (March 2014 Senate inquiry notes).

6.26 Dr Towler (then Principle Medical Adviser, Population Health Division, Dept of Health) went on to say: "There is no doubt that some of these medications that we suspect, because of the data that do not line up here, are being used inappropriately in terms of their funded indications on the PBS."

Recommendation 14

6.31 The committee recommends that the Commonwealth develop, in consultation with dementia advocates and service providers, guidelines for the recording and reporting on the use of all forms of restraints in residential facilities.

Recommendation 15

6.32 The committee recommends that the Commonwealth collect and report:

• the number of residents in aged care and acute care facilities with a diagnosis of dementia;

• the number of these residents who are taking, or have taken, antipsychotic medication;

Despite the Australian Senate 2014 inquiry, aged care and use of the antipsychotics for dementia in Australia has hardly changed in recent years. This is in spite of the many investigations and inquiries, including the more recent national framework for action on dementia (2015-2019) (Australian Health Ministers Advisory Council (AHMAC), 2015). Again, minimal recognition was given to the problems faced by overprescribing antipsychotic and related drugs for dementia. As the evidence below shows, corrective measures have not yet been successfully implemented to minimize the potential harm caused by prescribing such antipsychotic or related drugs.

Aged care and the use of antipsychotic drugs for dementia in the international setting – the UK helped to lead the way, but it still remains a major problem worldwide.

The UK took the initiative early on to review their aged care starting in 2003, and was proactive, leading the way in developing a national government policy - The National Clinical Practice Guideline Number 42, published in Nov. 2006 forming the basis that led later to instituting policies as part of a National Dementia Strategy Implementation Plan, developed in 2008 (released in Feb. 2009). The UK government backed action plan aimed at regulating and improving national health care for the elderly and included reducing use of antipsychotics in dementia patients. It coincided with the release of the Banerjee report (Banerjee, 2009) containing 11 recommendations aimed at reducing use of antipsychotic drugs to the level where the benefits outweighed risks in an attempt to assure that patients were managed more safely and effectively. In particular, an important part of this plan was the call for a cycle of audit and accountability that delivered good quality information specifically concerning the national use of antipsychotics for dementia and that could be applied to help drive down their use safely and drive up the quality of initiation, monitoring

and maintenance of these medications, only when they are needed. The Banerjee study (Banerjee, 2009) had shown that inappropriate prescribing in the elderly with such patients was associated with an 85% increased risk of adverse events and greater mortality.

USA policies and the follow-up to the Federal Food and Drug Administration (FDA) Black label warning – the ongoing saga to de-prescribe benzodiazepines and antipsychotic drugs for dementia

Despite early signs that the strong safety warnings and FDA black box labels were reducing the level of antipsychotic drug use for dementia (Kales et al., 2011), their use in nursing homes across the USA remained substantial for many years after the black box warnings—as evidenced by the 2011 audits from the Officer General of the US Federal Department of Health and Human Services (Levinson D.R., 2011). Based upon these and similar findings in Australia, Alzheimer's Australia concluded that antipsychotic drugs were commonly used as a form of chemical restraint, sedating residents so that not only their behaviours but also the underlying causes for those behaviours did not have to be addressed by staff (who were often overworked). They also concluded that apart from destroying social and emotional well-being, these drugs greatly increased risk of all-cause mortality including from stroke, heart attack, diabetes, Parkinsonism or falls resulting in serious life-threatening fractures. The May 2011 US Federal review (Levinson D.R., 2011) revealed that half of all Medicare claims for atypical antipsychotic drugs to elderly nursing home residents were inappropriate or erroneous and 88% were being used off-label directly contravening the black box warning that indicated increased risk of death in elderly patients with dementia-related psychosis and should not be taken by such patients, but were at an estimated annualized cost of US $232M in 2007 (Long Term Care Community Coalition (LTCCC), 2014a).

On March 29, 2012, the CMS federal agency within the United States Department of Health and Human Services administering the Medicare program, launched an initiative aimed at improving behavioural healthcare and safeguarding nursing home residents from the use of unnecessary antipsychotic medication. As part of the initiative, the CMS developed a national action plan with a multidimensional approach including public reporting, the raising of public awareness, regulatory oversight, and technical assistance/training and research (Centers for Medicare and Medicaid Services (CMS), 2012). This plan was targeted at enhancing person-centred care for nursing home residents, particularly those with dementia-related behaviours and reducing the percentage of long term care who receive antipsychotic medications reportedly by 25% by end of 2015 and down by 30% at the end of 2016 (Bakerjian, 2014). However, follow-up studies (Long Term Care Community Coalition (LTCCC), 2014a, 2014b; Singh & Nayak, 2015) showed that this initiative was not very successful because little change resulted in the general perception and consensus of antipsychotic drug therapy used in long-term care following its introduction (with the national average declining only from 23.6% to 19.1% by the end of 2014). In 2012, the CMS began reporting on their website about every nursing home and in 2015, set up a Five-Star Quality Rating System with regulations and fines for non-compliance. Recently, these and other measures have caused a decline in use, decreasing steadily over the intervening years so that at the end of 2016, it was reported as 16% (Gurwitz, Bonner, & Berwick, 2017). Similar problems have been reported in France (Gallini et al., 2014), the UK (Thompson Coon et al., 2014) and not just the USA (Gurwitz et al., 2017; Maust, 2016). Hence, Australia is not alone among countries worldwide dealing with the problems related to overprescribing antipsychotic drugs for dementia.

Class action law suits and fines as a warning have not been effective in reducing overprescribing

The situation arising after the US FDA black box labels led to class action law suits against Big Pharma. In 2009, Eli Lilly paid a $1.4B fine for aggressively marketing their atypical antipsychotic, Zyprexa (olanzapine) to elderly in long term care facilities. Sales of Zyprexa in 2008 were $2.2B in the US, and are close to $4.7B annually worldwide. At the time, the Office of Inspector General, U.S. Department of Health and Human Services said that this case would serve as a warning and preventative. However, several years later in Nov. 2013, in what the U.S. Department of Justice called "one of the largest health care fraud settlements in U.S. history," Johnson & Johnson and subsidiaries were fined more than $2.2B for the same aggressive marketing of antipsychotics for elderly care knowing that the FDA had indicated that these drugs were unsafe for the elderly. Allegedly, kickbacks were paid to physicians, as well as to Omnicare, the nation's largest long-term-care pharmacy provider who were recommending Johnson & Johnson's drugs, including risperidone (Risperdal), for use by nursing home residents. However, annual sales figures for risperdone are around the $4.5B annually in the USA over 2007-2009 and closer to $30B in worldwide sales. Hence, despite the fines and that these drugs have been contraindicated for elderly with dementia, their sales and large scale market profiteering continue to make this market a highly attractive one for Big Pharma.

USA policy and the CMS regulatory framework to reduce prescribing of psychotropic drugs.

In 2015, further reforms of the minimum health and safety standards in long-term care were initiated in the USA, involving public consultation and resulted in changes introduced into

the regulatory framework in October, 2016 (Centers for Medicare and Medicaid Services (CMS), 2016; Stefannaci, 2015). The bulk of aged care facilities in the USA currently fail to meet individualized quality of care mandated by federal requirements with considerable variation across nursing homes in use of such drugs reported recently and a call for a more systematic protocol guiding their use along with greater regulatory policies and enforcement (Cioltan et al., 2017). The CMS rule to be introduced in 3 phases over 2016-2019 will require:

1) that long-term care facilities ensure residents who have not used psychotropic drugs are not given them unless medically necessary.

2) that residents who use psychotropic drugs receive gradual dose reductions, and behavioural interventions, unless clinically contraindicated, in an effort to discontinue use of these psychotropic drugs.

3) to define “psychotropic drug” as any drug that affects brain activities associated with mental processes and behaviour.

4) that PRN (Pro re nata or as needed) orders for psychotropic drugs are limited to 48 hours. Orders cannot be continued beyond that time unless the primary care provider (for example, the resident's physician) reviews the need for the medications prior to renewal of the order, and documents the rationale for the order in the resident's clinical record.

The merits or not of the CMS definition of “psychotropic drug”, as opposed to use of the term “antipsychotic drug” are debatable because of problems arising given that some psychotropic drugs may prove to be beneficial, as has been the case for example with the

cholinesterase inhibitors such as donepezil, rivastigmine or galantamine for improving cognitive function in dementia, at least over months to years.

Increasing use of antipsychotic drugs for chemical restraint as exemplified by Australia. Can overprescribing be reduced by more effective means?

In Australia, according to recent statistics (Australian Institute of Health and Welfare (AIHW), 2014) from 2009-10, the Pharmaceutical Benefits Scheme (PBS) bill for the antipsychotics was nearly AUS $20M at 32.4% of the dementia drug total, whereas that for approved anti-dementia drugs such as donepezil (Aricept), memantine (Ebixa), rivastigmine (Exelon) or galantamine (Reminyl) was AUS $58.7M or 64% of the total benefit from dispensing by medical practitioners for dementia. In fiscal year 2013-2014, the antipsychotics bill grew to AUS $753M as 14% or 7.3 million government subsidized scripts, including for 1.1 million people aged 65 and over or 29% of this aged population (Australian Institute of Health and Welfare (AIHW), 2016a). Since 2010, nurse-aid practitioners have begun prescribing and the PBS registry shows the combined total cost of prescriptions by nurse-aid practitioners for risperidone and related metabolite paliperidone was nearly $0.5M (The Pharmaceutical Benefits Scheme (PBS), 2013, 2014, 2015). Over 2006-2015, continuing growth in prescribing was demonstrated for olanzapine, paliperidone, risperidone, clozapine and aripiprazole to nearly 4.75M scripts in 2015 (Drug Utilisation Sub-Committee (DUSC), 2016). Age-adjusted rates of antipsychotic prescribing increased with age, particularly in people aged 80 years or over, and most of the use in this age cohort was for risperidone to treat BPSD (Drug Utilisation Sub-Committee (DUSC), 2016). It was concluded that the data did not demonstrate a clear change in use between 2013 and 2015 in older people.

This continued use is despite positive outcomes for several initiatives targeted at reducing the use of antipsychotics in residential aged care (Drug Utilisation Sub-Committee (DUSC), 2016), with one called "RedUSe" showing reduced use was only short lasting (Westbury, Tichelaar, Peterson, Gee, & Jackson, 2011). The range of financial and economic data analyses suggests that the practices of prescribing antipsychotic drugs for dementia remains prevalent in Australia and are commonly used in spite of the overwhelming evidence for their significant risk of adverse effects. Confirmation has come from studies evaluating dispensing of psychotropic medications in Australia from January 2000 to December 2011 for the major classes of psychotropic medications (antidepressants, anxiolytics, sedatives, antipsychotics, mood stabilisers and attention-deficit hyperactivity disorder (ADHD) medications) based on data from the Drug Utilisation Sub-Committee of the Australian Department of Health and Ageing (Stephenson, Karanges, & McGregor, 2013). This report showed that dispensing of many atypical antipsychotics **tripled** over this period, including that of olanzapine, quetiapine, risperidone (doubling) and aripiprazole which all increased significantly, as did the benzodiazepine, alprazolam (doubling). Disturbingly, increased prescribing of antipsychotic drugs has been reported, including a doubling in prescriptions over the period from 2007 to 2015 within Australia, predominantly with 47.5% of single antipsychotic prescriptions being for haloperidol (Brett et al., 2017). Hence, it is clear that the message has not been getting through despite many reports published in Australian and other medical journals advising against their use (Loi SM, 2015; Looi, Byrne, Macfarlane, McKay, & O'Connor, 2014; Looi & Macfarlane, 2014) and medical advisories online from as early as 2013 (NPS Medwise, 2013). The reason for the systemic failure and continual increased use to treat the elderly with dementia is not through lack of publicizing the problem.

In August 2015, after drug company Janssen-Cilag, which developed risperidone, revealed adverse events data supplied to the Australian Therapeutic Goods Administration (TGA, the equivalent of the US FDA), based on a re-analysis of the results of trials conducted more than a decade beforehand indicated a more than fivefold higher risk of "cerebrovascular adverse events" — stroke or transient ischaemic attack — in patients with vascular or mixed dementia on risperidone. The TGA's new "indication" — or officially sanctioned use description — is that risperidone was indicated that it should be limited to 12 weeks use only in moderate to severe Alzheimer's dementia. Previously it had been indicated for other forms of dementia as well, with no time limit. In the UK, since 2005, risperidone was the only antipsychotic licensed for use in dementia and then, for periods of up to 6 weeks.

Examples where regulated central control has worked to force reduced prescribing

The Australian TGA acts in a regulatory capacity for drug scheduling via a national classification system that controls how medicines and chemicals are made available to the public. In 2013, the TGA attempted to move the entire benzodiazepine drug class as a Schedule 4 (requiring a doctor's prescription) to Schedule 8 restricted use drugs (requiring doctors to first obtain specific authority before use from the office of the Australian federal government Department of Human Services). However, the Australian Medical Association (AMA) protested that while benzodiazepines were at risk of abuse, there were currently a range of controls already in place, including electronic tracking of dispensing, patient and medical practitioner education, audits of prescribing, and prosecutions. In addition, the AMA argued, moving all benzodiazepines to Schedule 8 would create significant additional administrative burden for both hospital staff and doctors. After reviewing this and other submissions, the TGA decided that only alprazolam would be rescheduled from Schedule 4

to Schedule 8, while the scheduling of all other benzodiazepines remained unchanged. Alprazolam was rescheduled for several reasons, including the fact that overdoses of this drug resulted in increased morbidity and mortality, there had been rapid growth in its use, with evidence mounting of widespread misuse from drug abuse in Australia and hence, it was reclassified as a Schedule 8 drug from 1 February 2014. Nearly 500,000 prescriptions for alprazolam were written in 2013 which reduced to 265,000 in 2015, almost a 50% reduction within one year after reclassification (The Pharmaceutical Benefits Scheme (PBS), 2013, 2014, 2015). In a similar fashion, a reduction in the level of quetiapine prescribing occurred in Australia when this drug was restricted by changing from up to 5 repeats allowable to just a single script, no repeats allowed (Drug Utilisation Sub-Committee (DUSC), 2016).

Methods promoting compliance with de-prescribing of antipsychotics and benzodiazepines for dementia

The rapid reduction resulting from re-assigning and more restrictive drug re-scheduling as shown by the TGA in Australia above and the USA interventions by the CMS with the Five Star labelling of nursing homes and package of legislative regulations would suggest that regulatory reform can operate successfully if controlled via a central/federal facility to provide one effective mechanism promoting de-prescribing antipsychotic drugs for dementia. With current rapid email communication and electronic prescription, a system of checks and balances could be readily instituted, and ensure rapid responses to minimize the delays. Short term use may have to remain in place until improved substitute drugs are found. However, such a system of mandatory reporting and monitoring for the use of antipsychotics in dementia patients could help enforce de-prescribing. Even regulatory restrictions to short term use only (up to 48 hours as required by the new CMS regulations),

when doctors need to deal with the problems of treating BPSD where aggressive or violent outbursts occur may not be sufficient to promote de-prescribing such drugs. An electronic prescribing system might allow authorities an adequate regulatory monitoring and accountability to ensure compliance in the appropriate use of antipsychotic drugs and for corrective measures to be taken where use is deemed inappropriate or uncalled for. Calls have been made to remove any cost subsidies from the antipsychotics, should they be used for more than a certain period of time in an attempt to promote their de-prescribing.

Evidence from studies showing benefits from de-prescribing the antipsychotic drugs for dementia.

In 2012, the Halting Antipsychotic use in Long Term care (HALT) project was funded by the Australian Department of Social Services through the Aged Care Service Improvement and Healthy Ageing Grants Fund (Brodaty & Jessop, 2014). A targeted, evidence-based training package was developed to up-skill general practitioners and nursing home staff in this area, as well as in the quality use of medicines. The outcome of this study was first announced in the HALT September 2015 Newsletter (#06) and at a national conference in 2015 with follow-up of 76% of participants de-prescribed antipsychotics and 98% of those completely ceased (Jessop et al., 2017). Of these participants, 79% remained without this medication up to 12 months post cessation. Overall, no change in behavioural symptoms was noted amongst participants and many showed improvement.

These very positive outcomes from the HALT (Jessop et al., 2017) studies and the effects of regulating usage to de-prescribe drugs as discussed above support a role for government intervention and introducing policies and reform enforcing the de-prescribing of antipsychotics for dementia and other indications. Reclassification of these drugs using

Restricted Drug Classification Schedules requiring centralized authorization and approval can act as the checkpoint to ensure compliance. The evidence from the HALT and other related studies (Atti et al., 2013; Declercq et al., 2013; Gill & Seitz, 2013; Mace & Taylor, 2015; Plakiotis, Bell, Jeon, Pond, & O'Connor, 2015; Vasudev et al., 2015) all clearly support the importance of raising the general awareness across the health care system, particularly by prescribing doctors and via public education to expose the detrimental use of antipsychotics, and especially using benzodiazepine sedative type drugs in the elderly. Their use should be minimised such that they can only be applied under restricted/controlled situations where it is absolutely necessary and then, only for periods of short duration and with continued monitoring and review.

Alternative treatment methods should be actively sought and their use more strongly encouraged to treat dementia related behavioural problems (Hersch, 2008). In this regard, the tetracyclic antidepressants such as Trazodone might prove effective alternatives for treatment of BPSD (Henry, Williamson, & Tampi, 2011), and possibly used in combination with low-dose Lithium (Davangere P. Devanand et al., 2017). Several studies have suggested that tricyclic and related antidepressants may offer safer alternatives for use in the elderly (Coupland et al., 2011). In the Danish study, the tricyclic and related antidepressants were found among the least dangerous for dementia patients of all the psychotropics analyzed (Jennum, Baandrup, Ibsen, & Kjellberg, 2015).

Reducing the use of antipsychotic drugs and benzodiazepines for dementia has been a national priority in the UK (Banerjee, 2009; van Marwijk & Spiegel, 2009) and was a key element identified in the Dementia Plans for Wales (Welsh Assembly Government, 2010). National annual auditing of antipsychotic prescriptions for dementia in the UK from the NHS

Information Centre, 2012, reported a reduction by half between 2008 and 2011 and the national average was reported to be around 23% of all of the medications for dementia in 2015 (Mace & Taylor, 2015). However, conflicting data exists from 2007-2011 on use of antipsychotic drugs in primary health care in the UK, contrary to the best practice clinical guidance (Marston, Nazareth, Petersen, Walters, & Osborn, 2014).

In Canada, usage slightly reduced from 38% to 34% from 2004 to 2013, and for benzodiazepines decreased from 28% to 17% for dementia patients in long term care (Hersch, 2008). This may have resulted from the Canadian Deprescribing Network and developing guidelines to achieve this aim nationally with educational surveys of sixty-five Canadian geriatrics experts (Farrell et al., 2015). Given the significant increasing trend over 2000-2015 in Australia with dispensing of many antipsychotic drugs more than doubling (Drug Utilisation Sub-Committee (DUSC), 2016; Stephenson et al., 2013), it appears that antipsychotic drugs continue to be overprescribed for dementia in situations where they should be considered as neither necessary nor appropriate. In this regard, Australia appears to have a poorer record with increasing usage compared to other countries such as Canada, U.S.A. and the UK National Strategy linked reduction, based on greater accountability and monitoring.

Discussion and conclusions:

From the global evidence, it is clear that some valuable lessons can be learned from the mistakes made over the past decades, and since the 2009 Banerjee report (Banerjee, 2009) calling for solutions to the problem of overprescribing antipsychotics and other psychotropic drugs such as benzodiazepines for dementia and the best way to enforce changes in practice (Farrell et al., 2015). Whilst the evidence indicates that doctors should proceed with

extreme caution if prescribing for new users, they also have a duty of care to dementia patients in de-prescribing antipsychotic drugs for dementia. However, it is likely that it will require stronger leading roles played by central government interventions such as those exemplified by the CMS in the USA. The examples and evidence described herein support a case for central regulation to ensure that even greater reform takes place in clinical practice, and necessitating monitoring doctor/nursing home compliance and accountability in control of the use of antipsychotic drugs and benzodiazepines. It is readily apparent based on the information and growing volume of evidence above that prescribing for dementia is in need of such further reform worldwide. Whether greater control can be exerted to include their off-label use based on the failure of clinical guidelines alone is uncertain. The search for better alternatives needs to be actively encouraged. However, in order to improve existing national based systems for health care of the elderly with dementia, further changes will have to be made because the current situation shows little signs of working in a highly effective manner.

From the more successful strategies identified above, changes should include greater accountability by monitoring and regulations restricting use of the antipsychotics, benzodiazepines and related drugs for dementia, particularly in a way that better treatment alternatives can be actively sought and encouraged. The recently published clinical practice guidelines for dementia in Australia (Laver et al., 2016) are a step forward, but on the basis of the facts presented from the international range of sources as reviewed here, will be unlikely to have the desired outcomes with the failures of similar clinical guidelines elsewhere (UK and USA) in exerting any major influence or bringing about modified practices or greater compliance. The evidence is undeniable that the antipsychotic drugs

and the benzodiazepines in particular, when first administered carry a very high risk of serious adverse events. Also, when used for any length of time, they can be detrimental to the health of dementia patients and de-prescribing has been proven as highly beneficial.

One final point to consider is the emerging concept of “Elder Abuse” which is gaining acceptance worldwide and is now recognised by the World Health Organization as a problem (World Health Organisation (WHO), 2016). It is likely that it will not be long before misuse of chemical sedation with antipsychotics or other psychotropics/hypnotics such as the benzodiazepines for the elderly with dementia will become recognized and included in the list of criteria qualifying as having considerable potential for inclusion during screening for “Elder Abuse” in the aged care setting (Dong, 2015). Hence, the complex issues raised here should be tackled head-on as a worldwide health problem and perhaps will require legal reforms to be introduced “Halting Antipsychotic use in Long-Term” care or at least to attain the desired level of de-prescribing for this current widespread and often unnecessary practice as the easy fix option and simple remedy over the long term when dealing with the behavioural problems of dementia patients.

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