

DOCTOR OF PHILOSOPHY

Medication -related adverse events in
older people with dementia

causes and possible solutions

Ian Maidment

2013

Aston University

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Medication-related adverse events in older people with dementia; causes and possible solutions

Ian D Maidment,
Doctor of Philosophy

ASTON UNIVERSITY

May, 2013.

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Aston University

Abstract: Medication-related adverse events in older people with dementia; causes and possible solutions by Ian D Maidment for Doctor of Philosophy (2013)

This submission for a PhD by previously published work is based upon six publications in peer reviewed journals, reflecting a 9-year research programme. My research has shown, in a coherent and original way, the difficulty in treating people with dementia with safe and effective medication whilst providing research-founded guidance to develop mechanisms to optimise medication choice and minimise iatrogenic events. A wide range of methods, including systematic reviews, meta-analysis, randomised controlled trials (RCTs), quantitative research and mixed methods were used to generate the data, which supported the exploration of three themes.

The first theme, to understand the incidence and causes of medication errors in dementia services, identified that people with dementia may be more susceptible to medication-related iatrogenic disease partly due to inherent disease-related characteristics. One particular area of concern is the use of anti-psychotics to treat the Behavioural and Psychological Symptoms of Dementia (BPSD). The second and third themes, respectively, investigated a novel pharmacological and health services intervention to limit anti-psychotic usage. The second phase found that whilst the glutamate receptor blocker memantine showed some promise, further research was clearly required. The third phase found that anti-psychotic usage in dementia may be higher than official figures suggest and that medication review linking primary and secondary care can limit such usage.

My work has been widely cited, reflecting a substantial contribution to the field, in terms of our understanding of the causes of, and possible solutions to limit, medication-related adverse events in people with dementia. More importantly, this work has already informed clinical practice, patients, carers and policy makers by its demonstrable impact on health policy. In particular my research has identified key lines of enquiry for future work and for the development of my own personal research programme to reduce the risk associated with medication in this vulnerable population.

Dedication

To my parents, and Alison, William and Tomas; in the words of Po (Kung Foo Panda) – “There is no secret ingredient.”

Acknowledgements

I acknowledge the support and mentorship from Professors Mike Coleman and Keith Wilson.

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List of Key Abbreviations

ADEs	=	Adverse drug events
ADRs	=	Adverse drug reactions
ABC	=	Anti-cholinergic burden
BPSD	=	Behavioural and Psychological Symptoms of Dementia
CMAI	=	Cohen Mansfield Agitation Inventory
IIT	=	Investigator initiated trial
LASER-AD	=	London and South East Region AD study
MAGD	=	Memantine in AGitation in Dementia (clinical trial)
MMSE	=	Mini Mental State Examination
MRC CFAS	=	Medical Research Council Cognitive Function and Ageing Study
NPI	=	Neuro Psychiatric Inventory
NICE	=	National Institute for Clinical Excellence
NPSA	=	National Patient Safety Agency
NRLS	=	National Reporting and Learning System
OTC	=	Over-the-counter
PCT	=	Primary Care Trust
PRISMA	=	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QUOROM	=	Quality Of Reporting of Meta-analysis
RCT	=	Randomised controlled trial

1. Introduction

1.1. Definitions

There is a multiplicity of medication safety terms and a lack of standardisation (Yu et al, 2005), so it is therefore helpful to define the key medication safety terms.

- Adverse drug event (ADE): any iatrogenic harm related to medication and including harm due to adverse drug reactions and medication errors (Dean Franklin et al, 2005).
- Medication error: any error in any medication management process (Dean Franklin et al, 2005). A medication error is considered preventable and may or may not result in harm to a patient (Aronson, 2009).
- Adverse drug reaction (ADR): any response to medication that is unintended, noxious and occurring at doses utilised in humans for diagnosis, treatment or prophylaxis (Edwards et al, 2000). There is some confusion whether an ADR is preventable – this PhD follows the usual convection that ADRs are idiosyncratic and not preventable (Dean Franklin et al, 2005).

1.2. Background

“If medication related problems were ranked as a disease, it would be the fifth leading cause of death in the US” (Fick et al, 2003).

Medication is one of the main interventions within healthcare systems and it often transforms and saves lives (DoH, 2001a; Steinman et al, 2010). However, to achieve such positive outcomes the benefits must outweigh the risks (Bain et al, 2008; Garfinkel et al, 2010; Parsons et al, 2010; Schuling et al, 2012). A ‘risk benefit ratio’ can be assessed from the efficacy or effectiveness of the medication and the adverse event burden – any harm related to the medication (Dean Franklin et al, 2005; Steinman et al, 2010; Schuling et al, 2012). Adverse events include unforeseeable idiosyncratic reactions, but often patient harm results from medication errors (Bates et al, 1995; NPSA, 2009). Adverse drug events (ADEs) can have severe consequences and account for 6.5% of all admissions in England to secondary care facilities; the majority of these events were considered definitely or possibly preventable (Pirmohamed et al, 2004). Such events have been estimated to be responsible for 5,700 deaths each year in the UK and are economically costly to health service systems worldwide (DoH, 2001a;

Pirmohamed et al, 2004; Hug et al 2012). In the UK the annual costs associated with medication errors have been estimated at £2.4 billion (DoH, 2001b & 2004). More recently ADEs were associated with an adjusted increase in duration of hospital admission of 3.15 days and costs increased by US\$3420 (Hug et al, 2012).

Dementia has an estimated global prevalence of 35 million individuals (Alzheimer's Disease International, 2009). In the UK 700,000 people live with dementia - a figure which will double over the next 30 years as the population ages, reflecting global predictions (DoH, 2008a; Alzheimer's Disease International, 2009). People with dementia are commonly prescribed complex medication regimens, containing both physical and psychotropic medication and on average receive five different medicines (Schubert et al, 2006). Dementia is associated with significant morbidity and mortality, and therefore medication has the potential to significantly improve patient outcomes. However, frail older people with dementia may be particularly susceptible to medication-related harm (Gomez-Pavon et al, 2010; Steinman et al, 2010).

1.3. Published Papers

This PhD is based upon six publications in peer reviewed journals, which reflect my personal research programme over the previous nine years. These papers result from both national and international collaboration between practice and academia; I led on each of these research projects, or on a critical aspect. All the papers are co-authored and in accordance with the regulations I have clearly stated my contribution to the individual papers highlighting my role in the research. Of the six papers, I am first or senior author of five and had a key role in the remaining paper [see appendix 4 – for letters of attribution for papers (v) and (vi)]. Full copies of each paper are included in appendix 5.

Submitted Paper (i)

Maidment ID, Thorn A. 2005. A medication error reporting scheme – an analysis of the first 12-months. *Psychiatric Bulletin*, 25, 298-301

My role - conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (ii)

Maidment ID, Paton C, Lelliott P. 2006. A Review of Medication Errors in Mental Health Care. *Quality and Safety in Health Care*, 15, 409-13

My role - conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (iii)

Maidment ID, Haw C, Stubbs J, Fox C, Katona C, Dean-Franklin B. 2008a. Medication Errors in Older People with mental health problems: a review. *International Journal of Geriatric Psychiatry*, 23, 564-73

My role - conceived, designed and conducted the study, established and led research team, data analysis, lead and corresponding author.

Submitted Paper (iv)

Maidment ID, Boustani M, Rodriguez J, Brown R, Fox C, Katona C. 2008b. Efficacy of Memantine on Behavioral and Psychological Symptoms related to Dementia: A Systematic Meta-Analysis. *Annals of Pharmacotherapy*, 42, 32-38

My role - conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (v)

Fox C, Crugel M, **Maidment I**, Auestad BH, Coulton S, et al. 2012. Efficacy of Memantine for Agitation in Alzheimer's Dementia: A Randomised Double-Blind Placebo Controlled Trial. *PLoS ONE*. doi:10.1371/journal.pone.0035185

My role - significant and key involvement in concept, delivery, propagation. Jointly conceived the project. Overall responsibility for medication management including design of all medication management procedures to ensure successful study delivery. Also significantly contributed to the data interpretation, drafting of the manuscript and responding to referee's comments.

Submitted Paper (vi)

Child A, Clarke A, Fox C, **Maidment ID**. 2012. A pharmacy led program to review anti-psychotic prescribing for people with dementia. *BMC Psychiatry*. doi:10.1186/1471-244X-12-155.

<http://www.biomedcentral.com/1471-244X/12/155>

My role - significant and key involvement in concept and delivery; jointly conceived idea linking primary and secondary care to review medication including cross-boundary policy for the treatment of BPSD in primary care. During the project provided clinical supervision, advice on complex clinical scenarios and led the data analysis. Led on propagation; established publication team, and led and conducted data interpretation, drafting of the manuscript and responding to referee's comments.

These papers (i) to (vi) have been selected on the basis of a clearly identifiable contribution to the overall theme for the PhD, which is organised into three distinct, but linked, sub-themes. However, these papers only represent a proportion of my work and to provide a full further narrative I have reviewed, as required by the regulations (4.4. b. vii), papers (a) to (c) listed below, which are referenced, but not submitted as part of the PhD.

Referenced Paper (a) - section 2.5. (on page 17)

Maidment ID, Brown P, Calnan M. 2011a. An exploratory study of the role of trust in medication management within mental health services. *International Journal of Clinical Pharmacy*, 33, 614-20.

Referenced Paper (b) - section 5.5. (on page 31)

Fox C, Richardson K, **Maidment ID** et al. 2011a. Anticholinergic medication use and cognitive impairment in the older population: The MRC Cognitive Function and Ageing Study (CFAS). *Journal of the American Geriatric Society*. doi: 10.1111/j.1532-5415.2011.03491.x

Referenced Paper (c) - section 5.5. (on page 31)

Fox C, Livingston G, **Maidment ID** et al. 2011b. The Impact of anti-cholinergic burden in Alzheimer's Disease – the Laser AD study. *Age and Ageing*. doi: 10.1093/ageing/afr102

1.4. Research Themes

There are three distinct, but linked, themes within the overall submission and in a progressive manner the PhD considers the causes and frequency of medication error in dementia and then evaluates potential solutions to reduce iatrogenic medication-related adverse events. The first theme concentrates on understanding the key issues relating to medication error in dementia and obtaining baseline data on the causes and frequency, and includes an analysis of errors reported within a large mental health trust (i) and two systematic reviews (ii,iii). The subsequent themes focus on promising interventions to limit medication-related adverse events in older people with dementia. The second theme focuses on a novel pharmacological approach and includes a meta-analysis (iv) and a randomised controlled trial (RCT; v). The third section considers a novel health systems approach and includes a naturalistic evaluation of this approach (vi).

2. Research Theme 1 - Medication Error in Dementia

2.1. Objectives

To understand the frequency and causes of medication error in dementia.

2.2. Overview and Progression of Work

This section of the document is based upon the following three publications:

Submitted Paper (i)

Maidment ID, Thorn A. 2005. A medication error reporting scheme – an analysis of the first 12-months. *Psychiatric Bulletin*, 25, 298-301

Conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (ii)

Maidment ID, Paton C, Lelliott P. 2006. A Review of Medication Errors in Mental Health Care. *Quality and Safety in Health Care*, 15, 409-13

Conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (iii)

Maidment ID, Haw C, Stubbs J, Fox C, Katona C, Dean-Franklin B. 2008a. Medication Errors in Older People with mental health problems: a review. *International Journal of Geriatric Psychiatry*, 23, 564-73

Conceived, designed and conducted the study, established and led research team, data analysis, lead and corresponding author.

This project is grounded on clinical experience; my interest in medication error stemmed from my observations as an experienced clinical pharmacist working in dementia, that medication error in dementia is common, but under-reported; it is also associated with adverse patient-outcomes and potentially caused by specific factors. My first paper reported an analysis of medication errors in the first 12 months of a new medication error reporting scheme (Safemed) in a mental health trust (Maidment et al, 2005). Subsequently, I published the first systematic reviews, in the world, of medication error in mental health services (Maidment et al, 2006) and specifically in older people with mental health problems (Maidment et al, 2008a).

2.3. Impact of Publications

My work on medication error in dementia has had a significant impact and advanced the field. The publications have been widely cited in the research literature, including in subsequent reviews (Procyshyn et al, 2010 citing Maidment et al, 2006 and Maidment et al, 2008a; also see Appendix 2 for full details). The work has also been broadly cited outside the discipline including health informatics (Westbrook et al, 2010) and marketing (Tootelian et al, 2010); internationally (Quenon et al, 2009; Foppe van Mil, 2010) and in doctoral and masters levels theses (Navarro, 2009; Fernandez LLamazares, 2010; Shank, 2011).

The research has also informed health policy development. In 2007 the Healthcare Commission (predecessor organisation to the Care Quality Commission [CQC]), which promoted quality in healthcare by independently assessing standards, produced a landmark report on medication management within mental health services (Healthcare Commission, 2007). The report, citing work from both of my systematic reviews (Maidment et al, 2006; Maidment et al, 2008a), made a number of recommendations to improve medication management for people with dementia and mental health problems. The National Patient Safety Agency (NPSA) aims to improve patient safety by influencing, supporting and informing the healthcare sector. The 2007 annual report on the National Reporting and Learning System (NRLS; NPSA, 2009) contained a separate chapter on incidents from mental health organisations to help such organisations improve medication safety in dementia and mental health, and cited both systematic reviews.

2.4. Methods used

My initial research was to analyse medication errors and 'near misses' reported in a single trust using a mixed methods approach (Maidment et al, 2005). The reports collected demographic data, information on the reporting site, on the type and sub-type of the incident (based on NPSA categories), free text descriptions of the incident, contributing factors and preventative measures, and up to two potential causes from a pre-defined list of causes, informed by previous reports and the literature. An Access Database was established (by Angie Thorn – one of the co-authors of paper i) to electronically record the fields and the data was transferred to Excel to allow analysis (copy of excel data repository held by Ian Maidment). Descriptive statistics were generated for the type and sub-type of incident, site, cause and frequency of incident and inferential statistics were used to examine any relationship between the incident type, unit and severity. I rated the seriousness and likelihood of recurrence of

every incident was rated on a Likert scale of 1 to 5 based on NPSA rating scales (NPSA, 2008) and qualitatively analysed the free-text descriptions to identify the most frequent causes of errors.

With little data available from within a single organisation I led and conducted systematic reviews to summarise the available data on the incidence and causes of medication error within mental health and specifically dementia services (Maidment et al, 2006; Maidment et al, 2008a). I chose this approach, because systematic reviews can answer a clearly formulated research question, such as in this case; *what is the frequency and causes of medication error in dementia*, by identifying and collating data that meets *a priori* criteria and using explicit, systematic methodology to minimise bias (Liberati et al, 2009; Cochrane Collaboration, 2012). Such reviews enable researchers to identify key gaps in the academic literature and therefore priorities for future research including any interventional trials (Robinson et al, 2011).

The validity of a systematic review depends upon the ability to retrieve relevant data and both reviews used comprehensive search strategies (Maidment et al, 2006; Maidment et al, 2008a; Chan, 2012). However, due to resource limitations the reviews only searched for English language papers and therefore may have failed to identify non-English language studies. Furthermore, the systematic review in older people first identified studies focusing on mental health and then selecting data that included older people. A different set of studies may have been identified by focussing on older people first. Subsequent to the publication of the reviews PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidance has been developed to ensure that systematic reviews are fully and transparently reported (Liberati et al, 2009). Any subsequent update should follow this recent guidance.

2.5. Contribution and Contextualisation of Knowledge

a. Frequency of Medication Error in Dementia

The initial aspect of my work on medication error in dementia aimed to understand how commonly error occurred and obtain data on the frequency or incidence of these - the number of instances that the phenomenon occurs during a given period in a specified population (Noordzij et al, 2010). My initial analysis of medication errors reported within the mental health trust found that the frequency varied between different wards ranging from 0

to 0.4 reports per in-patient bed over the 12-month period although under-reporting was identified as a significant issue (Maidment et al, 2005). Both systematic reviews also found significant under-reporting (Maidment et al, 2006; Maidment et al, 2008a). This under-reporting, and methodological issues with the studies identified by both systematic reviews, made it impossible to calculate error rates and my findings on both issues are considered next.

My research found that under-reporting may significantly under-estimate the incidence of errors within dementia services (Maidment et al, 2005; Maidment et al, 2006; Maidment et al, 2008a). The analysis of medication incidents reported within the mental health trust appeared to identify significant under-reporting; five wards did not report any errors or near misses over 12-months, which is unrealistic given the context of medication usage in these wards (Maidment et al, 2005). The systematic reviews also identified under-reporting (Maidment et al, 2006; Maidment et al, 2008a). Under-reporting may be a particular issue in community environments; only 3 of 728 errors, identified by the systematic review of medication error in older people with mental health problems were recorded as occurring in the community, where most people with dementia receive treatment (Gisev et al, 2010 and Swaminath et al, 2010 citing Maidment et al, 2006; NPSA, 2009 citing Maidment et al, 2006 and Maidment et al, 2008a).

I identified that organisational culture may act as a potential barrier to reporting medication errors, particularly within mental health services (Maidment et al, 2005). Staff may be reluctant to report errors if an unsupportive or even hostile culture exists within the healthcare organisation towards learning from mistakes (Sarvadikar et al, 2010 citing Maidment et al, 2005). The analysis of the NRLS endorsed my earlier findings, on the importance of organisational culture and recommended that a culture which supported error reporting should be developed, to enable learning and therefore service improvement (NPSA, 2009). However, other authors have concluded that overall there is little data on the impact of organisational factors on medication error and further work is required (Ramsey et al, 2010 citing Maidment et al, 2006).

A lack of standardised methodological approaches made it difficult to compare studies and draw valid conclusions regarding overall frequency or incidence of medication error (Ramsey et al, 2010 and Lewis et al, 2009 citing Maidment et al, 2006). Studies used widely varying definitions of an error, and various data collection methods and denominators for calculating

the frequency or incidence of error (Lisby et al, 2010; Ramsey et al, 2010 and Lewis et al, 2009 citing Maidment et al, 2006). The number of written medication orders is generally considered the most useful denominator to calculate a measure of incidence although this measure also needs to be related to the average length of patient stay to understand the individual risk (Dean Franklin et al, 2005). Unfortunately, some studies identified by the systematic review used less meaningful denominators such as 'per unit time' without standardisation for the number of medication orders (Lisby et al, 2010; Ramsey et al, 2010 and Lewis et al, 2009 citing Maidment et al, 2006).

b. Causes of Medication Error in Dementia

To enable effective interventions to be developed the causes and factors that increase the risk of error need to be understood and this part of the PhD identified three key factors that may put people with dementia at a greater risk of medication-related adverse events (Maidment et al, 2005; Tootelian et al, 2010 citing Maidment et al, 2008a):

1. Complex regimens containing both physical (non-psychotropic) medicines and psychotropics.

One of my key findings, which provided the basis for future research, was that co-morbidity and the subsequent use of complex regimens may increase the risk of error (Navarro, 2009 citing Maidment et al, 2008a). The quantitative analysis, in the mixed methods study, found that moderate to severe incidents occurred disproportionately on older people's in-patient wards possibly due to the use of complex regimens containing both physical and psychotropic medicines (Maidment et al, 2005). This result, from a single organisation, was confirmed by my second systematic review, which found that regimen complexity; in particular the use of physical medicines increased the risk of error (Maidment et al, 2008a). Psychotropic medication regimens are also associated with error and my research identified that PRN (to be administered when required) psychotropic medication, such as treatments for agitation and behavioural problems, may be a particular problem (Baker et al, 2008 citing Maidment et al, 2006).

Such complex regimens may limit the ability of older people to safely self-medicate, increasing dependency and the risk of non-adherence; this non-adherence further increases the risk of a medication error (Murray, 2011 citing Maidment et al, 2008a; Ayalon et al, 2010 citing

Maidment et al, 2006). Input from experienced clinical pharmacists could optimise and simplify such complex regimens, however pharmacy services within dementia are generally poorly developed due to lack of investment (Maidment et al, 2006; Maidment et al, 2008a).

2. Complex care pathways, in elder care, involving many different health and social care professionals.

My research identified that the increasingly complex organisational structures providing dementia services could increase the risk associated with medication (Gisev et al, 2010 citing Maidment et al, 2006). Various health and social care staff provide care within newly established community teams and some of these staff lack basic knowledge in medication management, which increases the risk of error through poor decision making and limited monitoring of psychotropic medication (Duxbury et al, 2010 citing Maidment et al, 2006; Procyshyn et al, 2010 citing Maidment et al, 2008a). With this fragmentation of services, medication records need to be accurately shared between teams to avoid medication reconciliation-type errors (Gisev et al, 2010 citing Maidment et al, 2006). The primary / secondary care interface is a key care transition and within dementia services particularly associated with medication reconciliation-type errors (Gisev et al, 2010 citing Maidment et al, 2006; NPSA, 2009).

3. The impact of cognitive impairment, in someone with dementia, on the ability to self-advocate in relation to medication management.

James Reason developed the *Human Error Theory* based upon a systems approach to error and recognising that people are fallible and errors are likely to occur in any organisation (Reason, 1990). In the *Human Error Theory Swiss Cheese* model, errors occur when latent conditions, such as low staffing levels, create an environment where unsafe acts by people with direct patient contact are more likely to occur and, safeguards fail (Reason, 1990). People with dementia have reduced capacity, which may limit self-advocacy, and therefore under the *Human Error Theory*, one of the safeguards against an error, that is, the patient his or herself, is removed (Procyshyn et al, 2010 and Navarro 2009 citing Maidment et al, 2008a; Ayalon et al, 2010 citing Maidment et al, 2006). Put another way, someone with cognitive impairment, which is a characteristic symptom of dementia, may be less articulate and not be able to identify that he or she is about to receive the wrong medication (Navarro 2009 citing Maidment et al, 2008a).

This places greater responsibility, in many cases total responsibility, on others, clinicians and both formal and informal carers, to ensure safe medication management (Baker et al, 2009 and Duxbury et al, 2010 citing Maidment et al, 2006; Tootelian et al, 2010 citing Maidment et al, 2008a). However, empirical evidence suggests that embedding this change in care-giving dynamics into routine clinical practice may be problematic (Duxbury et al, 2010 citing Maidment et al, 2006). Qualitative analysis of the free-text comments relating to errors reported in a single trust identified the impact of cognitive impairment on patient safety [Data repository held by Ian Maidment relating to paper (i) – Maidment et al, 2005]. Incidents when support workers ‘run’ with the medication from the trolley and administer the medication to the wrong patient, typically occurred with agency staff unfamiliar with the ward, and when the patient was cognitively impaired and could not identify that he or she was about to receive the wrong medicine (Maidment et al, 2005). However, cognitive impairment was not generally identified as a cause of error, suggesting a lack of awareness of the impact of cognitive impairment on patient’s judgement and memory amongst frontline staff.

Limited self-advocacy may also be a risk factor for medication-related adverse events in other clinical areas notably paediatrics and mental health. Preventable adverse drug events were over twice as likely to occur in the children of parents who spoke English poorly, compared to the children of parents, who spoke English very well (OR, 2.3; 95% CI, 1.01-5.34; Zandieh et al, 2008). An exploratory qualitative study involving 3 focus groups containing patients (users of mental health services) found that a lack of trust, between the patient and clinician, increased the risk of medication-related adverse events (Maidment et al, 2011a). Even if the patient could articulate their concerns about medication due to this lack of trust clinicians may fail to fully address these concerns. The findings from this study in a single NHS trust require replication and expansion; in particular within black and ethnic minority populations. This study only examined trust from the perspective of the patient and a future study should triangulate data to examine trust from the clinician’s perspective.

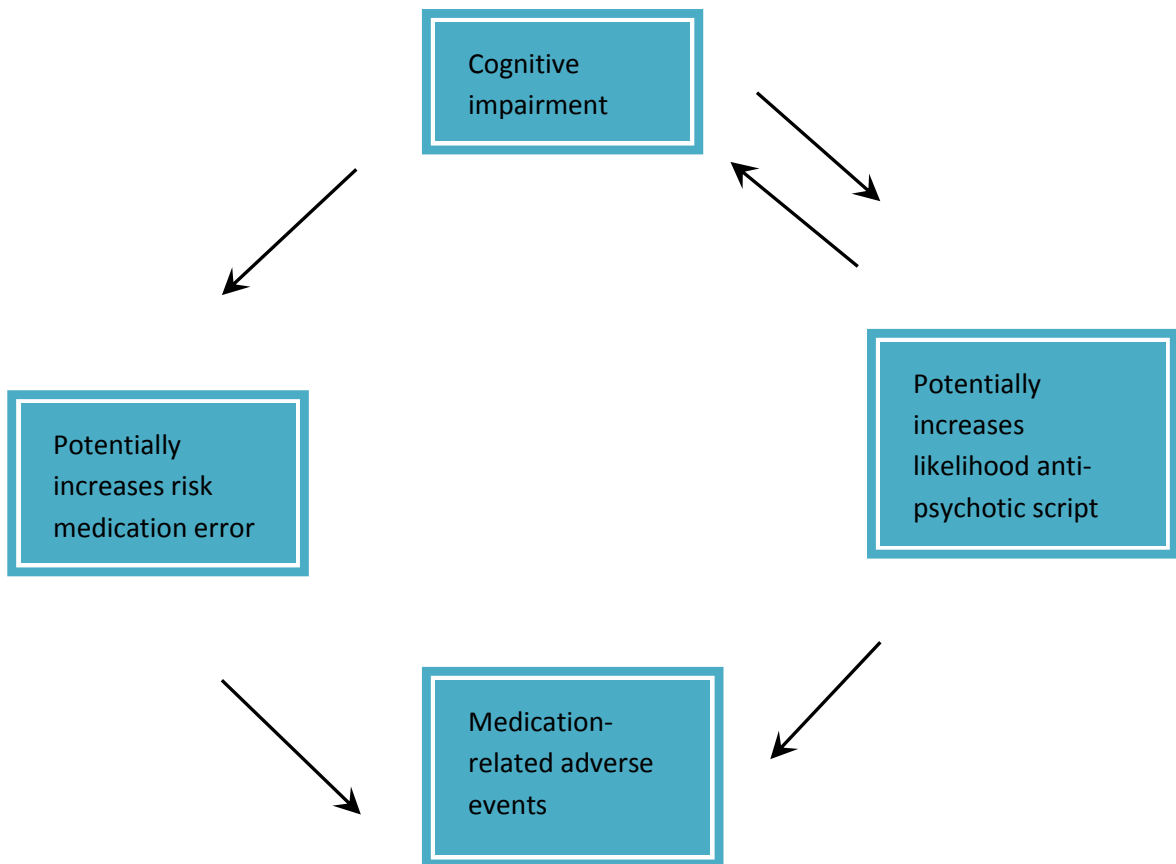
c. Cognitive Impairment and Anti-psychotic related adverse-events

My systematic reviews (Maidment et al, 2006; Maidment et al, 2008a) highlighted the need to understand the impact of cognitive impairment on the prevalence of medication-related adverse events. In 2009 the NPSA issued a report, which referenced both systematic reviews and highlighted this lack of understanding, of the impact of cognitive impairment on

medication-related adverse events, in policy terms. Behavioural and Psychological Symptoms of Dementia (BPSD) are amongst the most difficult symptoms of dementia to treat, and current treatments are controversial in that they are widely known to be associated with significant mortality (DoH, 2009). Anti-psychotics, the most widely used and the only licensed treatment for BPSD, are associated with 1,800 excess annual deaths; it has been estimated that 80% of such prescribing is inappropriate (DoH, 2008a; DoH, 2009). The next part of my work considers the impact of cognitive impairment on the management of the BPSD and medication-related adverse events.

Using the model developed earlier in this project, impaired cognition limits the ability of the person with dementia to self-advocate, so increasing their chances of receiving an anti-psychotic. In lay terms, someone with dementia may not be able to say “no” to an inappropriate anti-psychotic. Anti-psychotics in turn possess anti-cholinergic activity that can worsen cognition and therefore potentially increase the risk of a medication error. Figure 1 represents this complex relationship between anti-psychotics, cognitive impairment, and medication-related adverse events in dementia, highlighting that anti-psychotics potentially cause adverse-events via multiple, complex pathways.

Figure 1 - Relationship between anti-psychotics, cognitive impairment and medication-related adverse events in dementia



Having identified a previously unrecognised relationship by which impaired cognition in someone with dementia may increase the risk of medication error and medication-related adverse events associated with anti-psychotics, the next phase of the project investigated two strategies to limit the inappropriate and potentially harmful use of anti-psychotics. First, following NICE recommendations on future research priorities, the effect of memantine (a medicine licensed to treat the symptoms of moderate to severe dementia) was investigated, as an alternative pharmacological approach to anti-psychotics, with respect to controlling behavioural disturbances in dementia (NICE, 2006). Second, following recommendations by the Healthcare Commission (2007) and the European Federation of Nurse Researchers (Smith et al, 2008 citing Maidment et al, 2006) the effectiveness of a cross-boundary systems

approach, linking primary and secondary care pharmacy services, to limit the use of anti-psychotics, was investigated.

2.6. Summary

The initial theme of this project was to understand the frequency and causes of medication error in dementia. My research found that due to under-reporting, particularly from a community environment, and a lack of standardization, the true incidence of medication error in dementia remains largely unknown (Haw et al, 2007; Baker et al, 2008 & 2009 and Lisby et al, 2010 citing Maidment, et al 2006). I identified a clear 'signal' that due to multiple factors, including the complexity of care, lack of pharmacy input and the impact of cognitive impairment, people with dementia could be exposed to a greater risk of medication-related adverse events, and demonstrated the need for further research. This cognitive impairment could partly explain the frequent inappropriate usage of anti-psychotics in dementia.

Overall, this phase of my research demonstrated that medication error in dementia had been neglected by the research community; the frequency, causes and ways to reduce medication-related adverse events in people with dementia require further elucidation (NPSA, 2009 citing Maidment et al, 2006 and Maidment et al, 2008a; Baker et al, 2009 and Haw et al, 2007 citing Maidment et al, 2006). My subsequent research, which is described under phases two and three, investigated interventions to limit the usage of anti-psychotics in dementia and thereby reduce the risk of medication-related adverse events. Phase two focussed on a pharmacological intervention and phase three on an enhanced pharmacy role.

3. Alternative Pharmacological Approach to Treating BPSD

3.1. Objective

To develop an alternative pharmacological approach to treating BPSD.

3.2. Overview and Progression of Work

This section of the document is based upon the following two publications:

Submitted Paper (iv)

Maidment ID, Boustani M, Rodriguez J, Brown R, Fox C, Katona C. 2008b. Efficacy of Memantine on Behavioral and Psychological Symptoms related to Dementia: A Systematic Meta-Analysis. *Annals of Pharmacotherapy*, 42, 32-38

Conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (v)

Fox C, Crugel M, **Maidment I**, Auestad BH, Coulton S, et al. 2012. Efficacy of Memantine for Agitation in Alzheimer's Dementia: A Randomised Double-Blind Placebo Controlled Trial. *PLoS ONE*. doi:10.1371/journal.pone.0035185

Significant and key involvement in concept, delivery, propagation. Jointly conceived the project. Overall responsibility for medication management including design of all medication management procedures to ensure successful study delivery. Also significantly contributed to the data interpretation, drafting of the manuscript and responding to referee's comments.

Phase one identified that people with dementia may be at greater risk of medication-related adverse events partly due to cognitive impairment. One particular area of concern is the use of anti-psychotics. Therefore the research aim of the phase two studies was to develop an effective and safe alternative pharmacological intervention for the amelioration of BPSD that would limit the use of anti-psychotics reducing medication-related adverse events. Memantine had been suggested as a possible alternative to anti-psychotics for BPSD by NICE and therefore Phase two of the project investigated the efficacy of memantine for BPSD (NICE, 2006).

As the first stage of this theme, I formed and led, both supervising and doing the research, a multi-disciplinary, international team, linking practice with three academia departments, which conducted a systematic review and meta-analysis of the role of memantine in BPSD. The

team contained experts in clinical psychiatry (Chris Fox, UK), academic psychiatry (Cornelius Katona, UK), clinical pharmacy (Ruth Brown, UK), academic gerontology (Malaz Boustani, USA) and meta-analysis (Jorge Rodriguez, UK). Building on the meta-analysis and NICE guidance, which recommended that such a trial be conducted, I was a key part of a cross-disciplinary team, which designed and conducted the first worldwide RCT of Memantine in AGitation in Dementia (MAGD trial) a key BPSD symptom (Fox et al, 2012); I jointly conceived the project and led on medication management aspects of the design, development and conduct of the study.

3.3. Impact of Publications

My work on the appropriate treatment of BPSD has had a significant academic impact. The meta-analysis has been cited 38 times (Maidment et al, 2008a), and informed phase one animal studies (Filali et al, 2011 citing Maidment et al, 2008a) and training material produced by the BMJ group (Warner et al, 2008 citing Maidment et al, 2008a). The importance of the MAGD trial, which was fully published in May 2012, was highlighted by recent NICE guidance and the trial is likely to inform future policy as the first worldwide trial in this area (NICE, 2011). A poster of the trial received the American Geriatric Society presidential award in 2011 (American Geriatric Society, 2011).

3.4. Methods Used

NICE recommended that a RCT, studying the efficacy of memantine in BPSD should be conducted and the initial step to inform the need for the trial would usually be to review the evidence supporting the intervention (NICE, 2006; Canadian Institutes of Health Research, 2010). A meta-analysis, which involves the statistical combination of the results from studies to estimate effect, is usually the final part of a systematic review of the evidence (Moher et al, 1999). Meta-analyses may provide a more precise estimate of the effect of any intervention, because all the data from relevant trials is combined (Liberati et al, 2009). I led a systematic review / meta-analysis on the efficacy of memantine in BPSD (Maidment et al, 2008a).

Homogeneous results using the same outcome measure, the Neuro Psychiatric Inventory (NPI; Cummings et al, 1994) from five RCTs were included in the analysis (Maidment et al, 2008a). A modified QUOROM (Quality Of Reporting of Meta-analysis) approach was used including a Jadad quality assessment and informed the search strategy (Jadad et al, 1996; Moher et al,

1999). Myself and a colleague rated the quality of included trials; three RCTs scored two on the assessment (Jadad et al, 1996), had not been published in full and failed to supply complete information on randomisation, blinding and withdrawals (Warner et al, 2008 citing Maidment et al, 2008a). Importantly, the search strategy included searching the “grey literature” for example clinical trial registries (www.forestclinicaltrials.com) and conference proceedings, and identified data not accessible via MEDLINE.

Following the meta-analysis I was one of three clinicians, who jointly conceived a placebo-controlled RCT, generally considered the “Gold Standard” of evidence, in 2006 (Clay, 2010). This investigator initiated trial (IIT) – not initiated by a commercial sponsor - was conducted across 6 UK sites. IITs, like MAGD, are an important aspect of research, used to assess the off-label uses of licensed medicines and may be more impartial than commercially sponsored research (Arbit et al, 2006; Johnston et al, 2006; Health Canada, 2006). The research team received a “block grant” from the manufacturer and we developed the trial protocol and procedures ourselves. The Cohen Mansfield Agitation Inventory (CMAI; Cohen Mansfield et al, 1986; Cohen Mansfield et al, 1989) was the primary outcome, because agitation / aggression is considered the most clinically relevant BPSD symptom and associated with a poor quality of life and institutionalisation (Fox, 2011c; Fox et al, 2012). I led on pharmacy issues, designed and developed key medication management protocols and procedures, trained pharmacy staff and actively liaised with the manufacturer, clinical trials unit, randomisation service and six dispensing pharmacies to ensure compliance with GCP (Good Clinical Practice). Without my unique and specific contribution the research would not have successfully completed.

3.5. Contribution and Contextualisation of Knowledge

My work has significantly contributed to advancing the knowledge base on the treatment of BPSD, which is an international priority and the results need to be viewed in the context of both clinical and statistical significance. The meta-analysis found that, compared to placebo, memantine produced a statistically significant improvement in the NPI of 1.99 points (95% CI 0.08 to 3.91; $p=0.041$). However, the clinical significance, of a 2-point change in the NPI, was less clear (Dahl et al, 2008; Howland, 2008; Puangthong et al, 2009; Gellis et al, 2009; Robles, 2009; Balalle et al, 2010; Nourhashemi et al, 2010; Pinto et al, 2011 citing Maidment, et al 2008a). Therefore, the meta-analysis concluded that there was insufficient evidence to allow

clear recommendations on the role of memantine in the treatment of BPSD and that controlled clinical trials should be conducted (Maidment et al, 2008a).

One trial identified was excluded from the meta-analysis because only baseline data was reported (Bakchine et al, 2005). This trial, which was fully published after the meta-analysis had been completed, found that memantine failed to show any benefit against neuropsychiatric symptoms (Bakchine et al, 2008). If the study had been included in the meta-analysis, memantine may not have produced a statistically significant improvement in the NPI (Bakchine et al, 2008; Marum, 2009 citing Maidment et al, 2008a). However, rather than repeat the meta-analysis we conducted a definitive RCT.

Following recommendations from the meta-analysis, an RCT, MAGD, was conducted. The trial found that whilst memantine did not produce a statistically significant improvement in agitation, as measured by the CMAI (the primary measure), it did produce a statistically significant improvement in neuropsychiatric symptoms, rated by the NPI, a secondary measure. Results from RCTs need to be considered in a broader real-world context and, based on a minimum clinically important difference in the NPI of 8.0, the mean difference in the NPI change score between memantine and placebo of -9.6 (95% CI – 15.0 to – 4.3) was clinically significant (Cartwright et al, 2010; Howard et al, 2010). Therefore, future research should focus on the role of memantine against a broader cluster of neuropsychiatric symptoms, and because clinical trials do not allow testing the effects of different interventions in quick succession consider using a variety of methodological approaches (Cartwright et al, 2010; Clay, 2010; Mishra et al, 2012).

3.6. Summary

This phase aimed to limit the use of anti-psychotics in dementia, a key public health policy, by developing a new treatment for BPSD. Memantine effectively eased overall neuropsychiatric symptoms, but not specifically symptoms of agitation and therefore whilst memantine showed promise there was insufficient evidence from either the meta-analysis or the RCT to conclusively conclude that memantine was an effective treatment for BPSD. This research has made a substantial contribution to the advancement knowledge in the discipline by informing clinical practice and so health policy in this challenging clinical area of dementia. However, with the inconclusive result I decided to investigate other approaches to limiting the use of anti-psychotics for BPSD.

4. Alternative Health Systems Approach to Treating BPSD

4.1. Objectives

1. To obtain an accurate estimate of the usage of anti-psychotics in dementia across an entire healthcare organisation.
2. To evaluate a novel health systems approach to treating BPSD.

4.2. Overview and Progression of Work

This section of the document is based upon the following publication:

Submitted Paper (vi)

Child A, Clarke A, Fox C, **Maidment ID**. 2012. A pharmacy led program to review anti-psychotic prescribing for people with dementia. BMC Psychiatry. doi:10.1186/1471-244X-12-155.

<http://www.biomedcentral.com/1471-244X/12/155>

Significant and key involvement in concept and delivery; jointly conceived idea linking primary and secondary care to review medication including cross-boundary policy for the treatment of BPSD in primary care. During the project provided clinical supervision, advice on complex clinical scenarios and led the data analysis. Led on propagation; established publication team, and led and conducted data interpretation, drafting of the manuscript and responding to referee's comments.

This phase of the ongoing programme of research had two key objectives (Child et al, 2012). My 2006 study (Maidment et al, 2006) highlighted that primary care records may not accurately record psychotropic usage and the Healthcare Commission report (2007), which referenced this study and highlighted the lack of accurate data as a policy issue. More specifically and recently the National Dementia Strategy identified the need to obtain data on the level of use of anti-psychotics in BPSD (Do, 2008a). The first objective was therefore to obtain an accurate estimate of the usage of anti-psychotics in dementia, across an entire healthcare organisation.

The earlier phases of this project highlighted the potential role of pharmacy in limiting medication-related adverse events and the need to develop interventions to limit the use of anti-psychotics (Maidment et al, 2006 & 2008a). Building on recommendations from the Healthcare Commission Report, I wrote an invited editorial on the need for collaborative care

linking primary and secondary care, to optimise the use of psychotropics (Healthcare Commission, 2007; Maidment et al, 2007). Therefore, the second part of this phase evaluated the impact of such an intervention involving primary and secondary care, on the level of anti-psychotic prescribing in BPSD across a single PCT (Primary Care Trust). My role in this joint primary / secondary care project included significant involvement in the concept and delivery. I also led on propagation including publication of the work and have presented aspects of the work to various professional and research groups: South East England Clinical Pharmacy Group; British Geriatric Society meeting; invited guest lectures to Regenstrief Institute, Indiana University Health, Indianapolis and School of Pharmacy, Purdue University, West Lafayette, Indiana.

4.3. Impact of Publications

The paper describing phase three (Child et al, 2012), which was fully published in September 2012, had an immediate impact in both the lay and professional media.

Alzheimer's Research; <http://www.alzheimersresearchuk.org/news-detail/10570/Study-highlights-scale-of-challenge-to-reduce-antipsychotics-for-dementia/>

Alzheimer's Society;

http://www.alzheimers.org.uk/site/scripts/news_article.php?newsID=1362

Care industry news; <http://www.careindustrynews.co.uk>

Clinical Pharmacist; http://www.pjonline.com/clinical-pharmacist/2012_nov/antipsychotic_prescribing_levels_under_scrutiny

Daily Express; <http://www.express.co.uk/posts/view/352967/Shocking-rise-in-dementia-patients-on-zombie-drugs>

Daily Telegraph; <http://www.telegraph.co.uk/health/healthnews/9618466/Chemical-cosh-drugs-given-to-50pc-more-dementia-patients-than-thought.html>

Pharmaceutical Journal;

http://www.pjonline.com/news/pharmacist_input_reduces_antipsychotic_prescribing_for_patients_with_dementia

Science Codex;

http://www.sciencecodex.com/use_of_antipsychotic_drugs_by_people_with_dementia_under_reported-100325

Furthermore, according to the publisher's web-site

(<http://www.biomedcentral.com/bmcpsychiatry/>) throughout much of October and

November the article was the most viewed and forwarded article in BMC Psychiatry and I was interviewed live on BBC local radio about the findings.

4.4. Methods used

The analysis, which I led, used a quantitative approach to assess the extent of anti-psychotic prescribing for people with dementia and to evaluate the impact of a pharmacy-led programme to reduce such prescribing. The first part of this phase, to assess the extent of anti-psychotic prescribing for people with dementia, initially used the dementia registers to identify people within Medway PCT with a confirmed diagnosis of dementia. The individual patient record including the medication history of every person on the dementia register was then searched to identify people prescribed low-dose anti-psychotics, and which agent had been prescribed.

The second part of this phase evaluated the impact of a pharmacy-led programme to reduce such prescribing. The intervention was developed collaboratively linking my expertise with primary care and included three key aspects:

1. Myself and a PCT pharmacist (Anne Child) produced guidelines for primary care on the non-pharmacological and pharmacological management of BPSD (NHS Kent, 2011).
2. A clinical medication review, based on modified National Prescribing Centre Level three (Clyne et al, 2008) medication review criteria, delivered by an experienced senior clinical PCT pharmacist (Anne Child). (I provided clinical supervision including advice on individual cases, particularly regarding complex situations when the person with dementia was receiving multiple psychotropics). Withdrawal was generally considered if the patient was not under secondary care services, because this was considered too complex to pursue, was receiving the anti-psychotic for non-acute behavioural problems and the anti-psychotic had not been reviewed in the previous 12 months.

3. Education and support for unqualified formal carers, which was a recommendation from my systematic reviews submitted as part of this PhD via publication (Maidment et al, 2006; 2008a).

4.5. Contribution and Contextualisation of Knowledge

The research found 15.3% (161/1051) of people on the dementia register in Medway PCT were receiving anti-psychotics; this compares with a figure of 10.5% from a national audit (Personal Communication, Jonathan Hope, Principal Information Analyst at the NHS Information Centre). This is the first indication that official figures may under-estimate the use of anti-psychotics for people with dementia. The key strength of this project was that data on anti-psychotic usage was obtained from 98.3% of GP practices within Medway PCT, whereas the national study obtained data from 45.7% of practices nationally and 17.5% within Medway PCT. However, this project, like the national audit, may under-estimate anti-psychotic usage because it relied upon the accuracy of the dementia registers; only 43.8% of the expected numbers of people with dementia, in Medway, receive a formal diagnosis (Alzheimer's Society, 2012).

Amisulpride was the most commonly prescribed anti-psychotic, used in 52 of 161 (32.3%) people on the dementia register on anti-psychotics. However, amisulpride is unlicensed and the licensed product, risperidone, was only used in 23.0% of cases. Risperidone was the first anti-psychotic linked to excessive mortality in people with dementia and a failure to adequately publicise more recent guidance that all anti-psychotics carry a similar risk, may explain the high use of amisulpride. The guidelines, which were produced as part of this project, therefore highlighted that all anti-psychotics carry a similar risk of serious adverse events and risperidone was the only approved treatment (NHS Kent, 2011). Of the 161 people on the dementia register prescribed low-dose anti-psychotics, 87 were receiving on-going treatment from local secondary care mental health services and four from the local Learning Disability Teams. The anti-psychotic was either withdrawn, or the dosage was reduced, in 43 of the remaining 70 patients (61.4%).

Pharmacy services in dementia are poorly developed in the community with a shortage of experienced specialist clinical pharmacists and high levels of psychotropic usage (Maidment et al, 2006; Boardman et al, 2007; Patterson et al, 2010; Maguire et al, 2013). This study demonstrated that using the specialist secondary care workforce to outreach and link with primary care can reduce the use of anti-psychotics; such a concept is in-line with the recent

Pharmacy White Paper (DoH, 2008b). This concept should be developed and a future study should include a formal follow-up, validated assessment of the impact of the review, and include people with dementia also started on anti-psychotics by secondary care and other psychotropics, such as lorazepam, used in place of anti-psychotics.

4.6. Summary

This phase had two objectives; to obtain data on the extent of anti-psychotic prescribing in dementia and evaluate a novel health systems approach to reduce such usage. The study obtained data on the extent of anti-psychotic usage in dementia and found, as far as I am aware for the first time that official figures may under-estimate usage; this finding received widespread publicity in both the lay and professional media. Dementia registers were solely used to identify people with dementia and future research should estimate the extent of use of anti-psychotics in people with dementia, but lacking formal diagnosis.

The evaluation of the novel health systems approach, the second objective, showed that the intervention reduced the level of anti-psychotic prescribing. However, demonstrating a sustained long-term reduction was outside the scope of this practice-based project. Future research should also evaluate the impact of the review on the level of prescribing of alternative treatments to anti-psychotics such as benzodiazepines.

5. Medication Management in Dementia - Overview, Reflections and Critical Evaluation

5.1. Introduction

Section five will reflect on key aspects of medication management in dementia relating the findings from the publications contained within this PhD to wider aspects of medication management in dementia and highlighting future research priorities.

5.2. Medication error in dementia

My research found that a number of factors may increase the risk of medication error in people with dementia (Haw et al, 2007 citing Maidment et al, 2006; Procyshyn et al, 2010 and Tootelian et al, 2010 citing Maidment et al, 2008a). In particular, the cognitive impairment present in dementia appears to increase the risk of medication-induced iatrogenic disease, including adverse events associated with anti-psychotics, by limiting the ability of the patient to control their medication regimen (Navarro 2009 citing Maidment et al, 2008a; Ayalon et al, 2010 citing Maidment et al, 2006). However, cognitive impairment will potentially impact the capacity to manage all medication, not just anti-psychotics (Cotrell et al, 2006; Arlt et al, 2008; While et al, 2012). A holistic approach that considers both the impact of cognitive impairment on key aspects of medication management, including adherence and the role of the carers, and of medication on cognitive functioning will be needed to optimise the use of all medication in people with dementia. The next sections critically reflect on the broader impact of cognitive impairment.

5.3. Adherence

Cognitive impairment worsens adherence to medication (Cotrell et al, 2006; Farris et al, 2008). Medication management including responsibility for adherence moves from the personal responsibility of the person with dementia to an activity controlled by formal (paid) or informal (family) caregivers as the symptoms of dementia develop (Arlt et al, 2008; Farris et al, 2008). This change in role allocation may be sudden following a critical incident or more gradual (While et al, 2012; Thorpe et al, 2012). Education and simplifying the regimen, and critically support, both emotional and practical, from informal carers may increase adherence and help maintain independence (Hinkin et al, 2002; Maddigan et al, 2003; Kao et al, 2009; Scheurer et al, 2012). However, as I identified in an invited editorial, simply improving

adherence may be counter-productive and taking inappropriate medicines that are not required may increase the risk of medication-related iatrogenic disease (Maidment et al, 2011b). Therefore any intervention to improve adherence needs to be one element of a wider medication optimisation programme.

5.4. The role of carers in safe medication management

Both informal and formal carers have a key role in safe and effective medication management in dementia. Family carers may conduct up to ten medication management activities, every day, including managing side-effects and deciding whether to administer medication, and therefore have a key role in ensuring safe medication use (Francis et al, 2002; Smith et al, 2003). However, family carers do not feel equipped for such an enhanced medication management role and find the added responsibility a significant burden (Smith et al, 2003; While et al, 2012; Thorpe et al, 2012). The greater the number of medication related activities the greater the burden and the worse the social functioning of the family carer (Francis et al, 2002, Gort et al, 2007).

Someone with dementia is more likely to be admitted to residential care when their carer is burdened and stressed (Lieto et al, 2005). Therefore complex medication regimens, which are difficult for a carer to manage, could be implicated with the use of residential care (Lieto et al, 2005; Gort et al, 2007). Since 2010, I have led a research team, which has conducted exploratory qualitative research to develop understandings of the role of the family carer, and facilitators and barriers to effective discharge of this role; this research has recently been featured in an Alzheimer's Society newsletter (Nurock et al, 2012), presented internationally (invited presentation to the Regenstrief Institute, Indianapolis) and will form the basis for future grant applications.

5.5. Limiting the usage medicines that worsen cognition

There is increasing evidence that anti-cholinergics worsen cognition and I was a key collaborator and co-author of two longitudinal studies, which explored the impact of anti-cholinergic burden (ABC) on cognition function and mortality in older people (MRC CFAS [Medical Research Council Cognitive Function and Ageing Study; Fox et al, 2011a] and LASER-AD databases [London and South East Region AD study; Fox et al, 2011b]). These studies form part of my overall research theme and therefore, as per the regulations, are referenced and reviewed, but not presented as part of the overall submission.

The CFAS analysis found a high prevalence of anti-cholinergic usage (6,010 of 13,004 people on the database [48%] were receiving at least one medicine with anti-cholinergic activity) and a dose-dependent association between ABC and impaired cognition (Fox et al, 2011a). The greatest impact on cognition was found in people with mild symptoms of dementia (MMSE [Folstein et al, 1975; Mini Mental State Examination] – 26 to 30). The analysis also found, as far as we are aware, for the first time an association between cumulative anti-cholinergic burden and mortality; the odds of dying increased by 26% for each additional point on the ACB (OR = 1.26, 95% CI = 1.20-1.32).

The LASER-AD analysis failed to identify a link between ACB and either cognitive impairment and mortality (Fox et al, 2011b). However, the small sample size, there were only 224 participants, may explain the lack of evidence of any association (Fox et al, 2011b). The database also contains a population with moderate dementia and it has been postulated that a high anti-cholinergic burden is likely to exert a more profound and detectable impact on cognition in the earlier stages of dementia, rather than the later stages, where structure and function is already seriously eroded. Moreover, most of the academic literature supports the association between ACB and impaired cognition, yet despite this older people with dementia are commonly prescribed anti-cholinergics (Carriere et al, 2009; Jessen et al, 2010; Cai et al, 2012). The resultant cognitive impairment will worsen adherence and as discussed in phase one of this PhD limit self-advocacy potentially exposing the person with dementia to further adverse events.

5.6. The appropriate use of cognitive enhancers

A number of novel cognitive enhancers have and are likely to be marketed over the next five years including monoclonal antibodies, such as solanezumab and bapineuzumab, that bind to beta-amyloid (ClinicaSpace, 2012; The New York Times, 2012) and are administered by intravenous infusion, and the OTC (over-the-counter) nutritional supplement souvenaid® (Scheltens et al, 2012). These new treatments produce only modest improvements in cognition in people with mild dementia, and therefore people with dementia may receive increasingly complex regimens for cognitive enhancement, for example containing a nutritional supplement, a monoclonal antibody and an acetyl cholinesterase inhibitor. My research described in paper (vi) of this submission has demonstrated that collaborative care linking primary and secondary care pharmacy could deliver these complex pathways safely and

effectively. Community pharmacists in particular will have a key role in helping people with dementia and their carers manage these complex care pathways and optimising the use of cognitive enhancers.

5.7. Reflections on the Research

Reflection recognises the influence of the researcher on the project, the thinking underpinning the project, the approaches adopted and the outputs (Bryman, 2004; Kuper et al, 2008). It is also vital to reflect upon some of the key limitations. My focus on a pharmacological intervention and a pharmacy-led programme is linked to my personal biography and other interventions such as Health Informatics Systems may also be effective in supporting safe medication management (Westbrook et al, 2010 citing Maidment et al 2006). A pharmacist will always consider a pharmacological option and I have observed at first hand the need for clinical pharmacy, particularly in the community, to play a greater role in medication optimisation and improve outcomes. I worked in community pharmacy from 1988 to 1993 and more recently as a locum in 2011 when I observed a general lack of progress in developing a meaningful clinical role for community pharmacists.

It is also important to reflect on the research. The lack of data on medication error made it difficult to accurately estimate the frequency of medication error in dementia (Haw et al, 2007, , Gisev et al, 2010, Swaminath et al, 2010 and Harrison et al, 2011 citing Maidment et al, 2006). Further empirical work is required to enable a deeper understanding of the causes of medication error in dementia (Haw et al, 2007 citing Maidment et al, 2006; Procyshyn et al, 2010 and Tootelian et al, 2010 citing Maidment et al, 2008a). The results from both the interventional studies require confirmation; the exact role of memantine in BPSD requires further elucidation and the long-term impact of the pharmacy collaborative care model needs to be objectively evaluated.

5.8. Current and Future Work

My research that forms the basis of this submission has and will continue to help inform future research priorities including a future interventional study. Firstly, my work has shown that there is an urgent need for both exploratory qualitative and quantitative research on medication error in dementia, particularly the incidence, causes and the impact of cognitive impairment on safe medication management in the community environment where most people receive treatment (Haw et al, 2007, Gisev et al, 2010, Swaminath et al, 2010 and Harrison et al, 2011 citing Maidment et al, 2006). The impact of organisational factors on

medication error also needs to be understood (Haw et al, 2007; Baker et al, 2009 and Ramsey et al, 2010 citing Maidment et al 2006).

The key long-term objective must be to develop a model to enable the optimisation of medication use in people with dementia. Whilst the further exploratory work will help inform the development of the intervention the clear outline of the intervention is apparent from the results of both the pharmacological and the pharmacy-led studies, phases two and three of this PhD, and the subsequent detailed thoughts articulated earlier in section five of this PhD.

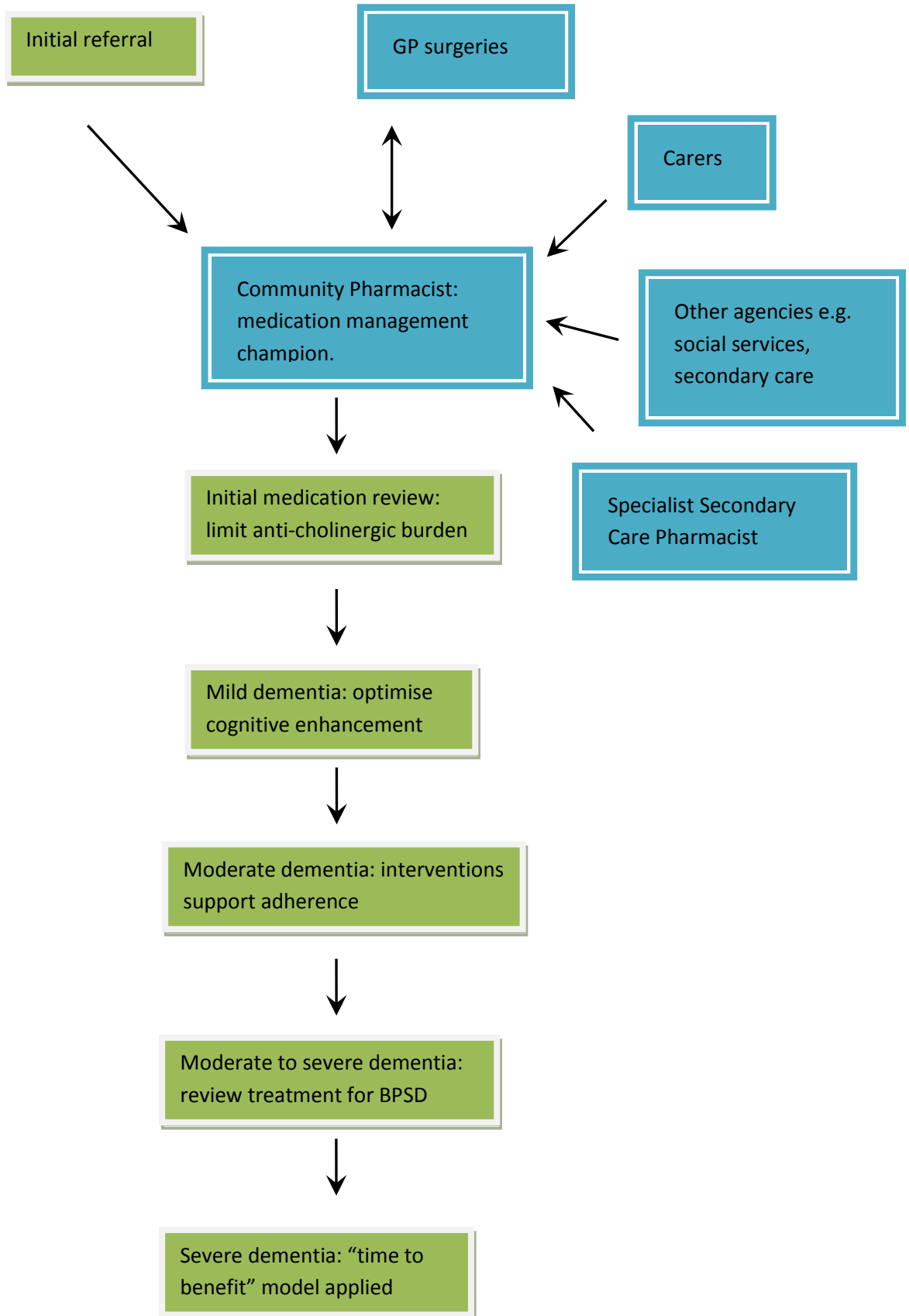
5.9. Proposed Enhanced Medication Optimisation Model in Dementia

The model should be based upon collaborative care and be delivered by community pharmacists, to ensure that it is widely accessible to the target population, but with appropriate support from specialist pharmacists (Duxbury et al, 2010 citing Maidment et al, 2006; Maidment et al, 2006). The community pharmacist, working very closely with the GP surgery and involving the person with dementia and carer as equal partners, will act as a “medication champion” to optimise medication use (Cotrell et al, 2006; Arlt et al, 2008; Farris et al, 2008; Avery et al, 2012; Thorpe et al, 2012). Again, this cross-sector collaborative approach, with carer involvement, reflects my employment background in both specialist care and community pharmacy, and also input from carers at the Alzheimer’s society (Nurock et al, 2012).

A multi-faceted intervention is more likely to improve outcomes and key aspects of the collaborative model will be regular full clinical medication reviews (type three) following initial assessment of medication appropriateness (see figure 2 for diagrammatic representation of care model). Once the regimen is appropriate interventions to monitor and facilitate adherence including regimen simplification and utilising mobile phone technology, can be implemented by the community pharmacist. The initial referral could occur when dementia is first diagnosed or alternatively a marker, such as a prescription for a cognitive enhancer, could trigger the referral. The community pharmacist should work with the carer and the person with dementia over a long period of time to provide continuity and enable a trusting relationship to develop (Maidment et al, 2011a).

Figure 2: Enhanced Medication Optimisation Model in Dementia

Key	
Blue box	Groups supporting collaborative care model
Green box	Aspects of intervention



Specific aspects of the intervention will depend upon the stage of the dementia. Initially, the intervention will involve limiting anti-cholinergic burden and supporting the use of treatments for mild dementia, such as souvenaid® and monoclonal antibodies. The community pharmacist will provide advice on the use of the OTC product souvenaid® including whether treatment is appropriate. Monoclonal antibodies were generally administered in acute hospitals in the clinical trials and community pharmacists may be able to support an alternative more cost-effective and convenient home delivery and administration model. Interventions to facilitate adherence should be applied as cognition worsens and the person with dementia struggles with self-medication.

Next, as the disease progresses to the moderate to severe stage the medication review should include the appropriate treatment of BPSD, which will involve two aspects, building on my work presented in this PhD. First, any pharmacy-led intervention should aim to limit the use of risk-laden and inappropriate psychotropics, anti-psychotics and other alternative inappropriate treatments, such as lorazepam. Second, the care pathway should support the use of potentially effective treatments such as memantine, ensuring that their usage in specific symptom clusters is based on the research evidence. Finally, in the severe stages of dementia, the concept of time-to-benefit should be applied, when only treatments that are likely to provide benefit are continued during the latter stages of life (Holmes et al, 2006; Parsons et al, 2012). Objective and validated measures including medication appropriateness, and rating scales for BPSD and quality of life should be used to assess the short and long-term impact of the collaborative model.

6. Concluding Statement

This submission has provided an overview of the findings from a series of published research studies on medication management in dementia. My work has shown, in a coherent and original way, the difficulty in treating people with dementia with safe and effective medication and by providing research-founded guidance, I have helped to develop mechanisms to optimise medication choice and minimise iatrogenic events. It is clear that people with dementia may be more susceptible to medication-related iatrogenic disease partly due to inherent disease-related characteristics in particular cognitive impairment. Limiting the use of anti-psychotics is a key Department of Health objective and this cognitive impairment could increase the risk that someone with dementia receives a potentially harmful anti-psychotic. Finally, I found that both an alternative pharmacological and a novel health service intervention could potentially reduce the level of use of anti-psychotics in BPSD.

This research is continuing to have impact through follow-on studies. Current research projects include an observational study on the role of pharmacy technicians in medication reconciliation in people admitted to Mental Health Trusts, including factors that increase the risk of discrepancies and a qualitative study on the role of community pharmacists in reducing the use of anti-psychotics in BPSD. However, the priority must be to develop an effective intervention and my work will continue to inform the further research required to enable effective interventions to be developed. I have submitted a grant application to formally test whether collaborative care linking primary and specialist secondary care pharmacy services can reduce the levels of psychotropic prescribing for BPSD. My longer-term objective is to develop a multi-faceted intervention, involving technology and carer empowerment, to improve the way that medication is managed for people with dementia. Pharmacy and particularly community pharmacy, has a key role in this sphere and needs to deliver an enhanced service to optimise medication use for people with dementia. People with dementia deserve the same standard of care as everyone else, yet my work has demonstrated that this is not consistently occurring; indeed, it is my belief based on my work in this area, that the research community needs to inform practice to deliver this key human right.

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Appendix 2 – Number of citations for the published papers

Please see below the number of citations for the journal articles included in this PhD via previously published work (source - <http://scholar.google.com/citations> - December 10th, 2012)

Maidment ID, Boustani M, Rodriguez J, Brown R, Fox C, Katona C. 2008. A systematic review of the use of memantine in agitation associated with dementia. <i>Annals of Pharmacotherapy</i> , 42, 32-38. ISSN 1060-0280.	38
Maidment ID, Paton C, Lelliott P. 2006. A Review of Medication Errors in Mental Health Care. <i>Quality & Safety in Health Care</i> , 15, 409-13. ISSN 1475-3898.	24
Maidment ID, Haw C, Stubbs J, Fox C, Katona C, Dean-Franklin B. 2008. Medication Errors in Older People with mental health problems: a review. <i>International Journal Geriatric Psychiatry</i> , 23, 564-73.	9
Maidment ID, Thorn A. 2005. A medication error reporting scheme – an analysis of the first 12-months. <i>Psychiatric Bulletin</i> , 25, 298-301, ISSN 0955-6036.	5
Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, et al. 2012. Efficacy of Memantine for Agitation in Alzheimer’s Dementia: A Randomised Double-Blind Placebo Controlled Trial. <i>PLoS ONE</i> 7(5): e35185. doi:10.1371/journal.pone.0035185	1

Appendix 3 – Letters of Attribution

Appendix 4 – Submitted Papers

Submitted Paper (i)

Maidment ID, Thorn A. 2005. A medication error reporting scheme – an analysis of the first 12-months. *Psychiatric Bulletin*, 25, 298-301

My role - conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (ii)

Maidment ID, Paton C, Lelliott P. 2006. A Review of Medication Errors in Mental Health Care. *Quality and Safety in Health Care*, 15, 409-13

My role - conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (iii)

Maidment ID, Haw C, Stubbs J, Fox C, Katona C, Dean-Franklin B. 2008a. Medication Errors in Older People with mental health problems: a review. *International Journal of Geriatric Psychiatry*, 23, 564-73

My role - conceived, designed and conducted the study, established and led research team, data analysis, lead and corresponding author.

Submitted Paper (iv)

Maidment ID, Boustani M, Rodriguez J, Brown R, Fox C, Katona C. 2008b. Efficacy of Memantine on Behavioral and Psychological Symptoms related to Dementia: A Systematic Meta-Analysis. *Annals of Pharmacotherapy*, 42, 32-38

My role - conceived, designed and conducted the study, established and led research team, analysed data, lead and corresponding author.

Submitted Paper (v)

Fox C, Crugel M, **Maidment I**, Auestad BH, Coulton S, et al. 2012. Efficacy of Memantine for Agitation in Alzheimer's Dementia: A Randomised Double-Blind Placebo Controlled Trial. PLoS ONE. doi:10.1371/journal.pone.0035185

My role - significant and key involvement in concept, delivery, propagation. Jointly conceived the project. Overall responsibility for medication management including design of all medication management procedures to ensure successful study delivery. Also significantly contributed to the data interpretation, drafting of the manuscript and responding to referee's comments.

Submitted Paper (vi)

Child A, Clarke A, Fox C, **Maidment ID**. 2012. A pharmacy led program to review anti-psychotic prescribing for people with dementia. BMC Psychiatry.

doi:10.1186/1471-244X-12-155.

<http://www.biomedcentral.com/1471-244X/12/155>

My role - significant and key involvement in concept and delivery; jointly conceived idea linking primary and secondary care to review medication including cross-boundary policy for the treatment of BPSD in primary care. During the project provided clinical supervision, advice on complex clinical scenarios and led the data analysis. Led on propagation; established publication team, and led and conducted data interpretation, drafting of the manuscript and responding to referee's comments.