University Hospitals Bristol NHS
NHS Foundation Trust

Dementia

Current Awareness Bulletin

Pharmacy and Medication Edition

NOVEMBER 2015

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November (1pm)

Weds 4th	**Literature Searching**
Thurs 12th	**Understanding articles**
Fri 20th	**Statistics**
Mon 23rd	**Literature Searching**

December (12pm)

Tues 1st	**Understanding articles**
Weds 9th	**Statistics**
Thurs 17th	**Literature Searching**

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New from Up-to-date

Cholinesterase inhibitors in the treatment of dementia

Authors: Daniel Press, MD: Michael Alexander, MD

Literature review current through: Oct 2015. | **This topic last updated:** Sep 28, 2015.

INTRODUCTION — Patients with Alzheimer disease (AD) have reduced cerebral production of choline acetyl transferase, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function. This early discovery of a marked cholinergic deficit in the brains of patients with AD led to the study of therapeutically augmenting cholinergic activity [1]. However, acetylcholine precursors were found to be ineffective, while postsynaptic cholinergic receptor agonists had unacceptable side effects. By contrast, cholinesterase inhibitors, which increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft, have a more favorable side effect profile and are of some benefit in patients with AD as well as other non-AD dementias, albeit modest in most cases.

Management of neuropsychiatric symptoms of dementia

Authors: Daniel Press, MD: Michael Alexander, MD

Literature review current through: Oct 2015. | **This topic last updated:** Oct 07, 2015.

INTRODUCTION — Neuropsychiatric symptoms in Alzheimer disease (AD) and other types of dementia are extremely common and often much more troubling than amnestic symptoms. This topic will review the causes and treatment of behavioral disturbance and other neuropsychiatric symptoms related to dementia.

Treatment of the cognitive features of dementia, the approach to safety and societal issues related to dementia, and the palliative care of patients with advanced dementia are discussed separately.

New from Cochrane Library of Systematic Reviews

Montreal Cognitive Assessment for the diagnosis of Alzheimer's disease and other dementias

Authors: Daniel HJ Davis, Sam T Creavin, Jennifer LY Yip, Anna H Noel-Storr, Carol Brayne, Sarah Cullum

First published: 29 October 2015Full publication history

Assessed as up-to-date: 2 August 2012

Editorial Group: Cochrane Dementia and Cognitive Improvement Group

Abstract

Background: Dementia is a progressive syndrome of global cognitive impairment with significant health and social care costs. Global prevalence is projected to increase, particularly in resource-limited settings. Recent policy changes in Western countries to increase detection mandates a careful examination of the diagnostic accuracy of neuropsychological tests for dementia.

Objectives: To determine the diagnostic accuracy of the Montreal Cognitive Assessment (MoCA) at various thresholds for dementia and its subtypes.

Rivastigmine for Alzheimer's disease

Authors; Jacqueline S Birks, Lee Yee Chong, John Grimley Evans

First published: 22 September 2015Full publication history

Assessed as up-to-date: 2 March 2015

Editorial Group: Cochrane Dementia and Cognitive Improvement Group

Abstract

Background: Alzheimer's disease is the commonest cause of dementia affecting older people. One of the therapeutic strategies aimed at ameliorating the clinical manifestations of Alzheimer's disease is to enhance cholinergic neurotransmission in the brain by the use of cholinesterase inhibitors to delay the breakdown of acetylcholine released into synaptic clefts. Tacrine, the first of the cholinesterase inhibitors to undergo extensive trials for this purpose, was associated with significant adverse effects including hepatotoxicity. Other cholinesterase inhibitors, including rivastigmine, with superior properties in terms of specificity of action and lower risk of adverse effects have since been introduced. Rivastigmine has received approval for use in 60 countries including all member states of the European Union and the USA.

Objectives: To determine the clinical efficacy and safety of rivastigmine for patients with dementia of Alzheimer's type.

Current Awareness Database Articles on Dementia

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This edition of the Dementia Current Awareness Bulletin focus on the latest peer reviewed evidence relating to those providing care and support.

Title: Effects on Symptoms of Agitation and Depression in Persons With Dementia Participating in Robot-Assisted Activity: A Cluster-Randomized Controlled Trial

Citation: Journal of the American Medical Directors Association, October 2015, vol./is. 16/10(867-873), 1525-8610;1538-9375 (01 Oct 2015)

Author(s): Joranson N., Pedersen I., Rokstad A.M.M., Ihlebaek C.

Abstract: Objectives: To examine effects on symptoms of agitation and depression in nursing home residents with moderate to severe dementia participating in a robot-assisted group activity with the robot seal Paro. Design: A cluster-randomized controlled trial. Ten nursing home units were randomized to either robot-assisted intervention or a control group with treatment as usual during 3 intervention periods from 2013 to 2014. Setting: Ten adapted units in nursing homes in 3 counties in eastern Norway. Participants: Sixty residents (67% women, age range 62-95 years) in adapted nursing home units with a dementia diagnosis or cognitive impairment (Mini-Mental State Examination score lower than 25/30). Intervention: Group sessions with Paro took place in a separate room at nursing homes for 30 minutes twice a week over the course of 12 weeks. Local nurses were trained to conduct the intervention. Measurements: Participants were scored on baseline measures (T0) assessing cognitive status, regular medication, agitation (BARS), and depression (CSDD). The data collection was repeated at end of intervention (T1) and at follow-up (3 months after end of intervention) (T2). Mixed models were used to test treatment and time effects. Results: Statistically significant differences in changes were found on agitation and depression between groups from T0 to T2. Although the symptoms of the intervention group declined, the control group's symptoms developed in the opposite direction. Agitation showed an effect estimate of -5.51, CI 0.06-10.97, P =048, and depression -3.88, CI 0.43-7.33, P =028. There were no significant differences in changes on either agitation or depression between groups from T0 to T1. Conclusion: This study found a long-term effect on depression and agitation by using Paro in activity groups for elderly with dementia in nursing homes. Paro might be a suitable nonpharmacological treatment for neuropsychiatric symptoms and should be considered as a useful tool in clinical practice.

Title: Clinical and imaging correlations of generalized hypersynchronous alpha activity in human EEG recordings, during alertness

Citation: Journal of Clinical Neurophysiology, October 2015, vol./is. 32/5(413-418), 0736-0258;1537-1603 (01 Oct 2015)

Author(s): Katsavos S., Artemiadis A., Tsivgoulis G., Kararizou E., Papadopoulos G., Triantafyllou N.

Abstract: Purpose: In a considerable percentage of individuals with a detectable alpha rhythm in their EEG, bursts of generalized hypersynchronous alpha activity (GHSAA) may occur, during alertness. The aim of this study was to examine whether appearance of GHSAA, which probably generates from transcortical circuitry, shows any correlation with demographic characteristics, underlying normal or abnormal pathophysiology, or substances in use. Methods: The authors retrospectively reviewed 441 EEG recordings performed in their laboratory during a 1-year period for presence of GHSAA, concomitantly collecting data that concerned symptoms, diagnosis, imaging, medication, and demographics. Recordings in mental states other than alertness were excluded from the sample. Results: Generalized hypersynchronous alpha activity was found in 22.95% of the study population. Its occurrence was diminished in male gender (P , 0.001), older age (Kendall tau, 0.16; P , 0.0001), and disorders involving structural abnormalities like brain lesions or neurodegeneration (P , 0.02). Dementia, Parkinson disease, and psychoses showed individually a trend towards lower GHSAA presence. Conclusions: In the sample, the presence of GHSAA was commonly observed in the cohort of patients without abnormalities in their neuroimaging studies. Generalized hypersynchronous alpha activity is a finding of youth and requires a properly functioning cerebral cortex in order to emerge. Female preponderance may signify underlying trangender differences in alpha rhythm generators. These preliminary results indicate that the significance of GHSAA alterations deserves more thorough evaluation in larger groups of patients suffering from a variety of different neuropsychiatric disorders.

Title: Approaches to gradual dose reduction of chronic off-label antipsychotics used for behavioral and psychological symptoms of dementia

Citation: Consultant Pharmacist, October 2015, vol./is. 30/10(599-611)

Author(s): Tjia J., Reidenberg M.M., Hunnicutt J.N., Paice K., Donovan J.L., Kanaan A., Briesacher B.A., Lapane K.L.

Abstract: OBJECTIVE: Little is known about how to best taper antipsychotics used in patients with dementia. To address this gap, we reviewed published antipsychotic discontinuation trials to summarize what is known about tapering strategies for antipsychotics used with older adults with dementia. We further developed pharmacokinetic-based gradual dose reduction (GDR) protocols based on antipsychotic half-lives. DATA SOURCES: MEDLINE, EMBASE, and International Pharmaceutical Abstracts were searched up to October 2014 to identify intervention studies reporting the behavioral and psychological symptoms of dementia outcomes resulting from discontinued off-label use of antipsychotics in nursing facility populations. Recently published pharmacokinetic reviews and standard pharmacology texts were used to determine antipsychotic drug half-lives for the pharmacokinetic-based GDR protocols. STUDY SELECTION: For the review, studies with an intervention resulting in antipsychotic medication discontinuation or tapering were eligible, including randomized controlled trials and pre- and post-intervention studies. DATA

EXTRACTION: When available, we extracted the protocols used for antipsychotic GDR from each study included in the review. DATA SYNTHESIS: We found that clinical trials used different approaches to antipsychotic discontinuation, including abrupt discontinuation, slow tapers (more than two weeks), and mixed strategies based on drug dosage. None of the published trials described an approach based on pharmacokinetic principles. We developed a two-stage GDR protocol for tapering antipsychotic medications based on the log dose-response relationship; each stage was designed to result in a 50% dose reduction prior to discontinuation. This pharmacologically based strategy for patients chronically prescribed antipsychotics resulted in recommendations for slow tapers. CONCLUSION: Our theoretically derived GDR recommendations suggest a different approach than previously published in clinical trials. Further study is needed to evaluate the effect of this approach on patients.

Title: Combined therapy of Di-Huang-Yi-Zhi with Donepezil in patients with Parkinson's disease dementia

Citation: Neuroscience Letters, October 2015, vol./is. 606/(13-17), 0304-3940;1872-7972

Author(s): Gu C., Shen T., An H., Yuan C., Zhou J., Ye Q., Liu T., Wang X., Zhang T.

Abstract: Here we conducted a randomized and double-blind study attempting to explore the safety and efficacy of combined therapy of Di-Huang-Yi-Zhi (DHYZ) with donepezil in treating Parkinson's disease dementia (PDD). Sixty PDD patients were included and randomly divided into control group and DHYZ group. All patients were given donepezil (5. mg last for a month, then 10 mg for the rest months, once daily), while patients in DHYZ group were additionally administrated with DHYZ (150 ml, twice daily). The measurement subjects included mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), the Barthel Index for activities of daily living (ADL) and Traditional Chinese medical (TCM) symptoms before and after treatment in this study. The whole study lasted for six months. Significant differences were observed on MMSE, MoCA, ADAS-Cog, ADL and TCM in both control and DHYZ group ($P< 0.05$ or $P< 0.01$) before and after drug treatment. Furthermore, there were more obvious changes of MMSE, MoCA, ADAS-Cog, ADL and TCM scores compared the DHYZ group with the control group ($P< 0.01$) which suggested the DHYZ group showed a more effective improvement on cognition, behavior as well global function. In conclusion, the combined therapy of DHYZ with donepezil showed a more effective improvement in PDD and the underlying mechanism may be related to the synergic amelioration of cholinergic system between them.

Title: Alzheimer's disease progression model using disability assessment for dementia scores from bapineuzumab trials

Citation: Alzheimer's and Dementia: Translational Research and Clinical Interventions, October 2015, vol./is. 1/2(141-149), 2352-8737 (15 Oct 2015)

Author(s): Xu S.X., Samtani M.N., Russu A., Adedokun O.J., Lu M., Ito K., Corrigan B., Raje S., Brashear H.R., Styren S., Hu C.

Abstract: Objective Disability assessment for dementia (DAD) measurements from two phase-3 studies of bapineuzumab in APOE epsilon4 noncarrier and carrier Alzheimer's disease (AD) patients were integrated to develop a disease progression model. Methods We evaluated longitudinal changes in DAD scores, baseline factors affecting disease progression, and bapineuzumab effect on disease progression. Results A beta regression model best described DAD disease progression. The estimated treatment effect of bapineuzumab was not significant, consistent with lack of clinical efficacy observed in the primary analysis. The model suggested that progression of DAD tended to decrease with increase in bapineuzumab exposure. The exposure-response relationship was similar regardless of APOE epsilon4 status but more pronounced in patients with mild AD. Baseline disease status, age, memantine use, and years since onset (YSO) had significant effects on baseline DAD scores. AD concomitant medication use, baseline disease status, and YSO had significant effects on disease progression rate, measured by DAD score. Conclusions The beta regression model is a sensible modeling approach to characterize functional decline in AD patients. This analysis suggested a possible effect of bapineuzumab exposure on DAD progression. Further evaluation may be warranted in future studies. Trial Registration ClinicalTrials.gov identifier: NCT00575055 and NCT00574132.

Title: Re-engineering a neuroprotective, clinical drug as a procognitive agent with high in vivo potency and with GABAA potentiating activity for use in dementia

Citation: BMC Neuroscience, October 2015, vol./is. 16/1, 1471-2202 (October 19, 2015)

Author(s): Luo J., Lee S.H., VandeVrede L., Qin Z., Piyankarage S., Tavassoli E., Asghodom R.T., Aissa M.B., Fa M., Arancio O., Yue L., Pepperberg D.R., Thatcher G.R.J.

Abstract: Background: Synaptic dysfunction is a key event in pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD) where synapse loss pathologically correlates with cognitive decline and dementia. Although evidence suggests that aberrant protein production and aggregation are the causative factors in familial subsets of such diseases, drugs singularly targeting these hallmark proteins, such as amyloid-beta, have failed in late stage clinical trials. Therefore, to provide a successful disease-modifying compound and address synaptic dysfunction and memory loss in AD and mixed pathology dementia, we repurposed a clinically proven drug, CMZ, with neuroprotective and anti-inflammatory properties via addition of nitric oxide (NO) and cGMP signaling property. Results: The novel compound, NMZ, was shown to retain the GABA_A potentiating actions of CMZ in vitro and sedative activity in vivo. Importantly, NMZ restored LTP in hippocampal slices from AD transgenic mice, whereas CMZ was without effect. NMZ reversed amnestic blockade of acetylcholine receptors by scopolamine as well as NMDA receptor blockade by a benzodiazepine and a NO synthase inhibitor in the step-through passive avoidance (STPA) test of learning and working memory. A PK/PD relationship was developed based on STPA analysis coupled with pharmacokinetic measures of drug levels in the brain: at 1nM concentration in brain and plasma, NMZ was able to restore memory consolidation in mice. Conclusion: Our findings show that NMZ embodies a promising pharmacological approach targeting synaptic dysfunction and opens new avenues for neuroprotective intervention strategies in mixed pathology AD, neurodegeneration, and dementia.

Title: Risk of dementia in elderly patients with the use of proton pump inhibitors

Citation: European Archives of Psychiatry and Clinical Neuroscience, October 2015, vol./is. 265/5(419-428), 0940-1334;1433-8491 (24 Oct 2015)

Author(s): Haenisch B., von Holt K., Wiese B., Prokein J., Lange C., Ernst A., Brettschneider C., Konig H.-H., Werle J., Weyerer S., Luppa M., Riedel-Heller S.G., Fuchs A., Pentzek M., Weeg D., Bickel H., Broich K., Jessen F., Maier W., Scherer M.

Abstract: Drugs that modify the risk of dementia in the elderly are of potential interest for dementia prevention. Proton pump inhibitors (PPIs) are widely used to reduce gastric acid production, but information on the risk of dementia is lacking. We assessed association between the use of PPIs and the risk of dementia in elderly people. Data were derived from a longitudinal, multicenter cohort study in elderly primary care patients, the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe), including 3,327 community-dwelling persons aged >75 years. From follow-up 1 to follow-up 4 (follow-up interval 18 months), we identified a total of 431 patients with incident any dementia, including 260 patients with Alzheimer's disease. We used time-dependent Cox regression to estimate hazard ratios of incident any dementia and Alzheimer's disease. Potential confounders included in the analysis comprised age, sex, education, the Apolipoprotein E4 (ApoE4) allele status, polypharmacy, and the comorbidities depression, diabetes, ischemic heart disease, and stroke. Patients receiving PPI medication had a significantly increased risk of any dementia [Hazard ratio (HR) 1.38, 95 % confidence interval (CI) 1.04-1.83] and Alzheimer's disease (HR 1.44, 95 % CI 1.01-2.06) compared with nonusers. Due to the major burden of dementia on public health and the lack of curative medication, this finding is of high interest to research on dementia and provides indication for dementia prevention.

Title: Mild Cognitive Impairment in newly diagnosed Parkinson's disease: A longitudinal prospective study

Citation: Parkinsonism and Related Disorders, October 2015, vol./is. 21/10(1219-1226), 1353-8020;1873-5126 (01 Oct 2015)

Author(s): Santangelo G., Vitale C., Picillo M., Moccia M., Cuoco S., Longo K., Pezzella D., di Grazia A., Erro R., Pellecchia M.T., Amboni M., Trojano L., Barone P.

Abstract: Introduction: In PD, Mild Cognitive Impairment (PD-MCI) occurs since early stages of disease. The aims were to assess presence of PD-MCI in untreated, drug-naive PD patients, and to follow-up the sample over 4 years to ascertain evolution of neurocognitive profile. Methods: Seventy-six patients underwent neuropsychological testing at baseline (T0), and after 2 (T1:n = 62) and 4 years (T2:n = 55). Diagnosis of PD-MCI and PD-associated dementia (PDD) was made according to current consensus criteria. Results: PD-MCI occurred in 25/76 patients (32.9%) at baseline, and 4 of them reverted from PD-MCI to Normal Cognition (Reverters), 7 remained stable (Non-Reverters) and 2 developed PDD at T2; 12 patients were lost to the follow-up. Among the 51 patients with normal cognition (PD-CN) at T0, 27 had normal cognition at T2 (5 of them were Reverters with respect to diagnosis at T1), 5 had MCI at T1 and T2 (Non-Reverters), 9 had MCI at T2 only, whereas 1 developed PDD; 9 patients were lost to the follow-up.At baseline, Reverters (n = 9) had

younger age at onset and better performance on constructional visuospatial task than Non-Reverters (n = 12). Compared to patients without PD-MCI at all evaluations (n = 19), Reverters had poorer performance on verbal immediate recall and attention tasks and higher level of apathy at T0. Reduced performance on the Stroop Test at baseline predicted PD-MCI at T2. Conclusion: Executive dysfunctions predicted development of PD-MCI after few years from onset. Reversal from PD-MCI to PD-CN was related to young age at onset and high level of apathy at baseline evaluation.

Title: Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: Systematic review and meta-analysis

Citation: British Journal of Psychiatry, October 2015, vol./is. 207/4(293-298), 0007-1250;1472-1465 (01 Oct 2015)

Author(s): Orgeta V., Qazi A., Spector A., Orrell M.

Abstract: Background Anxiety and depression are common in people with dementia and mild cognitive impairment (MCI), but there is uncertainty about the effectiveness of both pharmacological and psychological therapies. Aims To evaluate the evidence of effectiveness of psychological treatments in treating depression and anxiety in people with dementia and MCI. Method We carried out a systematic review and meta-analysis of randomised controlled trials (RCTs) of psychological treatment versus usual care in people with dementia and MCI. Primary outcomes were symptoms of anxiety and depression. Secondary outcomes were quality of life, ability to perform daily activities, neuropsychiatric symptoms, cognition and caregivers' self-rated depressive symptoms. Results We included six RCTs, involving 439 participants with dementia, which used cognitive-behavioural therapy, interpersonal therapy, counselling or multimodal interventions including a specific psychological therapy. We found beneficial effects for both depression and anxiety. Overall, the quality of the evidence was moderate for depression and low for anxiety, due to the methodological limitations of the studies we identified and the limited number of trials. Conclusions The evidence from six RCTs suggests that psychological treatments are effective in reducing symptoms of depression and anxiety for people with dementia. There is a need for high-quality, multicentre trials including standardised, well-defined interventions.

Title: General practitioners adherence to recommendations from geriatric assessments made during teleconsultations for the elderly living in nursing homes

Citation: Maturitas, October 2015, vol./is. 82/2(184-189),

Author(s): Georgeton E., Aubert L., Pierrard N., Gaborieau G., Berrut G., De Decker L.

Abstract: Objectives To determine the factors associated with general practitioners adherence to recommendations from geriatric assessments made during teleconsultations for the elderly living in nursing homes. Study design Prospective cohort study in three nursing homes in Vendee, France, with access to teleconsultations from Challans Hospital. Teleconsultations with geriatric assessment for which recommendations were made by a geriatrician (n = 69). Main outcome measurements Participants were separated into two groups based on the evidence of general practitioners adherence to recommendations 30 days after teleconsultation. Their adherence has been defined by the application by

themselves supporting the elderly of prescription or organization of all recommendations made by the geriatrician during the teleconsultation. The type of recommendations was pharmacological and non-pharmacological treatments, and expert medical advice. The recorded data included the main reason of teleconsultation's request, age, sex, dementia diagnosis, multimorbidities scale, body mass index, Activities of Daily Living Scale, 4-items Geriatric Depression Scale, existence of a fall, and the Neuropsychiatric Inventory. Logistic regressions were performed to examine the factors associated with general practitioners adherence to recommendations from the geriatric assessment. Results General practitioners adherence to recommendations was made for 58 teleconsultations (86.3%). A fully adjusted logistic regression showed that general practitioners adherence to recommendations was associated with risk of depressive syndrome (OR = 8.00, P = 0.040) and expert medical advice's recommendations (OR = 17.97, P = 0.040). Conclusions General practitioners adherence to recommendations from the geriatric assessment made during teleconsultations for elderly living in nursing homes is associated with the risk of depressive syndrome's existence and the expert medical advice recommendations.

Title: Adverse drug reactions in special populations - The elderly

Citation: British Journal of Clinical Pharmacology, October 2015, vol./is. 80/4(796-807),

Author(s): Davies E.A., O'Mahony M.S.

Abstract: The International Conference on Harmonization considers older people a 'special population', as they differ from younger adults in terms of comorbidity, polypharmacy, pharmacokinetics and greater vulnerability to adverse drug reactions (ADRs). Medical practice is often based on single disease guidelines derived from clinical trials that have not included frail older people or those with multiple morbidities. This presents a challenge caring for older people, as drug doses in trials may not be achievable in real world patients and risks of ADRs are underestimated in clinical trial populations. The majority of ADRs in older people are Type A, potentially avoidable and associated with commonly prescribed medications. Several ADRs are particularly associated with major adverse consequences in the elderly and their reduction is therefore a clinical priority. Falls are strongly associated with benzodiazepines, neuroleptics, antidepressants and antihypertensives. There is good evidence for medication review as part of a multifactorial intervention to reduce falls risk in community dwelling elderly. Multiple medications also contribute to delirium, another multifactorial syndrome resulting in excess mortality particularly in frail older people. Clostridium difficile associated with use of broad spectrum antibiotics mainly affects frail older people and results in prolonged hospital stay with substantial morbidity and mortality. Antipsychotics increase the risk of stroke by more than three-fold in patients with dementia. Inappropriate prescribing can be reduced by adherence to prescribing guidelines, suitable monitoring and regular medication review. Given the heterogeneity within the older population, providing individualized care is pivotal to preventing ADRs.

Title: Converting maslinic acid into an effective inhibitor of acylcholinesterases

Citation: European Journal of Medicinal Chemistry, October 2015, vol./is. 103/(438-445),

Author(s): Schwarz S., Loesche A., Lucas S.D., Sommerwerk S., Serbian I., Siewert B., Pianowski E., Csuk R.

Abstract: During the last decade, maslinic acid has been evaluated for many biological properties, e.g. as an anti-tumor or an anti-viral agent but also as a nutraceutical. The potential of maslinic acid and related derivatives to act as inhibitors of acetyl- or butyryl-cholinesterase was examined in this communication in more detail. Cholinesterases do still represent an interesting group of target enzymes with respect to the investigation and treatment of the Alzheimer's disease and other dementia illnesses as well. Although other triterpenoic acids have successfully been tested for their ability to act as inhibitors of cholinesterases, up to now maslinic acid has not been part of such studies.For this reason, three series of maslinic acid derivatives possessing modifications at different centers were synthesized and subjected to Ellman's assay to determine their inhibitory strength and type of inhibitory action. While parent compound maslinic acid was no inhibitor in these assays, some of the compounds exhibited an inhibition of acetylcholinesterase in the single-digit micro-molar range. Two compounds were identified as inhibitors of butyrylcholinesterase showing inhibition constants comparable to those of galantamine, a drug often used in the treatment of Alzheimer's disease. Furthermore, additional selectivity as well as cytotoxicity studies were performed underlining the potential of several derivatives and qualifying them for further investigations. Docking studies revealed that the different kinetic behavior within the same compound series may be explained by the ability of the compounds to enter the active site gorge of AChE.

Title: Sialic acid (SA)-modified selenium nanoparticles coated with a high blood-brain barrier permeability peptide-B6 peptide for potential use in Alzheimer's disease

Citation: Acta Biomaterialia, October 2015, vol./is. 25/(172-183),

Author(s): Yin T., Yang L., Liu Y., Zhou X., Sun J., Liu J.

Abstract: The blood-brain barrier (BBB) is a formidable gatekeeper toward exogenous substances, playing an important role in brain homeostasis and maintaining a healthy microenvironment for complex neuronal activities. However, it also greatly hinders drug permeability into the brain and limits the management of brain diseases. The development of new drugs that show improved transport across the BBB represents a promising strategy for Alzheimer's disease (AD) intervention. Whereas, previous study of receptor-mediated endogenous BBB transport systems has focused on a strategy of using transferrin to facilitate brain drug delivery system, a system that still suffers from limitations including synthesis procedure, stability and immunological response. In the present study, we synthetised sialic acid (SA)-modified selenium (Se) nanoparticles conjugated with an alternative peptide-B6 peptide (B6-SA-SeNPs, a synthetic selenoprotein analogue), which shows high permeability across the BBB and has the potential to serve as a novel nanomedicine for disease modification in AD. Laser-scanning confocal microscopy, flow cytometry analysis and inductively coupled plasma-atomic emission spectroscopy ICP-AES revealed high cellular uptake of B6-SA-SeNPs by cerebral endothelial cells (bEnd.3). The transport efficiency of B6-SA-SeNPs was evaluated in a Transwell experiment based on in vitro BBB model. It provided direct evidence for B6-SA-SeNPs crossing the BBB and being absorbed by PC12 cells. Moreover, inhibitory effects of B6-SA-SeNPs on amyloid-beta peptide (Abeta) fibrillation could be demonstrated in PC12 cells and bEnd3 cells. B6-SA-

SeNPs could not only effectively inhibit Abeta aggregation but could disaggregate preformed Abeta fibrils into non-toxic amorphous oligomers. These results suggested that B6-SA-SeNPs may provide a promising platform, particularly for the application of nanoparticles in the treatment of brain diseases. Statement of Significance Alzheimer's disease (AD) is the world's most common form of dementia characterized by intracellular neurofibrillary tangles in the brain. Over the past decades, the blood-brain barrier (BBB) limits access of therapeutic or diagnostic agents into the brain, which greatly hinders the development of new drugs for treating AD. In this work, we evaluated the efficiency of B6-SA-SeNPs across BBB and investigated the interactions between B6-SA-SeNPs and amyloid-beta peptide (Abeta). We confirm that B6-SA-SeNPs could provide a promising platform because of its high brain delivery efficiency, anti-amyloid properties and anti-oxidant properties, which may serve as a novel nanomedicine for the application in the treatment of brain diseases.

Title: Transfer of care from hospital to community pharmacy-into action during Spring to Green

Citation: International Journal of Pharmacy Practice, October 2015, vol./is. 23/(101-102)

Author(s): Wilcock M., Davidson I., Yelling P.

Abstract: Focal points * To assess transfer of care (ToC) activity if the clinical pharmacy team is able to refocus its work onto ward-based patient facing tasks. * The number of monthly ToC increased three- to six-fold compared to previous months. * Over a two week period in excess of 200 patients were approached for a ToC service that did not progress to completion. Introduction Medication discrepancies may occur at transitions in care, especially for patients discharged from hospital. Targeted Medicines Use Review (tMUR) and New Medicines Service (NMS) offer an opportunity to encourage patients to attend community pharmacy for a post discharge medicines check-up, though it is recognised that the potential of community pharmacy to improve patient safety after hospital discharge is not being utilised.1 For nearly two years our hospital pharmacy has supported the take up of this transfer of care (ToC) service by signposting patients to their community pharmacy after discharge. At admission, when medicines reconciliation is undertaken, the ToC service is explained to the patient and consent sought to fax their discharge medication details to their regular community pharmacy. As part of the fax, the community pharmacist is asked to fax back to the hospital what action, if any, has been taken (e.g. tMUR, NMS, advice given). Approximately 2000 patients are discharged monthly from the hospital but the clinical pharmacy team has struggled to achieve more than 50 ToC instances per month. Reasons for this are thought to be issues of time and motiva- tion for the ward-based pharmacy team. 'Spring to Green' fortnight in February 2015 was an opportunity for the hospital to deliver services in an innovative manner aimed at improving the bed state and patient care. Methods During this Spring to Green period, the pharmacy clinical team spent a much greater proportion of their time on the wards focusing on patient safety work, medicines reconciliation, and ToC. Any non-patient facing work (e.g. meetings) was cancelled and less manpower time was spent in the dispensary. As well as encouraging and recording the uptake of ToC, we also started to capture details on the number of patients who were unable to provide consent to ToC or who were asked but refused consent. This is quality improvement and evaluation and ethics committee approval was not needed. Results The

'Spring to Green' fortnight and continuation of that model of pharmacy practice throughout all February substantially increased the number of information transfers to pharmacies compared to baseline data from previous months (see Table 1). During the main two weeks in February, a further 213 patients were approached for ToC but consent was not obtained. Reasons for ToC not progressing were varied and included the patient: declining the service (41%), suffering confusion/ dementia (20%), registered to receive their medicines from a dispensing surgery (20%), being acutely ill (15%), not taking regular medication at discharge (4%). Discussion We have shown that new ways of working for the clinical pharmacy team can increase the number of patients accessing our ToC process. How sustainable this model will be in the longer term is to be explored. Though the hospital pharmacy can increase its ToC output, we still have little documented evidence of the value of this service locally as the number of community pharmacy returns remains low. We do now have a better understanding of why some patients are not eligible for ToC. (Table Presented).

Title: Understanding the type of queries and interventions made within a community pharmacy for patients with cognitive impairment and the related resource required

Citation: International Journal of Pharmacy Practice, October 2015, vol./is. 23/(89-90),

Author(s): Manrai E., Urban R., Fox F.

Abstract: Focal points * To determine the type of interventions made within community pharmacy for patients who have cognitive impairment, plus the time and resource required to resolve these interventions. * The total time spent resolving issues equated to 181.6 hours per year with a substantial number of queries from patients needing clarification about their medication. * Further work is required to understand the resource implications of the growing population of patients with cognitive impairment. Introduction Many patients need support when taking their medication, especially those who are easily confused or who have cognitive impairment. There is increasing work which looks at the impact of patients with cognitive impairment and dementia on health care services.1 However, there is no work investigating the impact of these patients within community pharmacy. This audit investigates whether relevant information was recorded each time an intervention was made for patients with cognitive impairment, identifies the number and type of interventions made and records the time spent resolving issues. Methods Within the pharmacy each patient who received a monitored dosage system (MDS) had a pre-existing individual patient record card in addition to their electronic patient medication record. These record cards were routinely used to record information regarding the patient's medication plus all interventions made by pharmacy staff. A separate intervention form was developed for the study to record interventions for patients not on a MDS, which included the same information. Patients were included if they received an MDS and/or they had a diagnosis of dementia. All patient medication record cards and intervention forms were reviewed to identify interventions made within a 6 week period between October 2014 and December 2015. Each intervention was audited against organisational policy for recording interventions to determine whether any details were omitted. This included the patient details, date of intervention, person to whom intervention was discussed, person making the intervention, job role of staff member making the intervention and action required. The interventions were also thematically analysed by the investigator to identify types of intervention recorded, then each type of intervention quantified. The total time spent

working on the intervention was also measured and recorded by the member of staff making the intervention. Ethical approval was not needed as this was deemed audit and service improvement. Results During the audit period 102 interventions were made; mean 17 interventions per week. Patient details and intervention were always documented. The recording of the name and job role of the person making the intervention was 89% (91/102) and 77% (78/102) respectively. The outcome/action taken was recorded on 88% (90/102) of occasions. Least recorded was the person with whom the intervention was discussed (55%, 56/102). These omissions occurred on the patient record cards rather than the intervention records made for non-MDS patients as the intervention form prompted the completion. The commonest intervention was dose alterations (16.7%, 17/102), followed by patient confusion about delivery dates (15.7%, 16/102) (see fig 1). Most interventions were made by a technician (87.2%, 89/102). The total amount of time spent by staff resolving interventions for MDS patients was 975 minutes and non-MDS patients 282 minutes; total 1257 minutes over 6 weeks. This equates to 10894 minutes per year (181.6 hours) or approximately 1/2 a day per week. Discussion Patients with cognitive impairment need substantial time and input from community pharmacy staff to help them to optimise their medication. Improvement recording the detail of the interventions is needed to ensure a clear audit trail of interventions made. Further work is required to understand the applicability to other community pharmacies and resource implications of the growing population for patients with cognitive impairment. (Figure Presented).

Title: Reviewing the continued need for pharmacotherapy in the treatment of urinary incontinence

Citation: International Journal of Pharmacy Practice, October 2015, vol./is. 23/(85-86),

Author(s): Hall J., Bryson G.

Abstract: Focal points * Trial stop of medication to treat urinary incontinence to determine continued need for treatment * Out of 70 of the patients asked to trial a stop in treatment ~73% remained stopped after an eight week period * An estimated annual saving of 14,542 was achieved for the practice involved Introduction Urinary incontinence (UI) is a common symptom that can be caused by one or more underlying conditions. It has a wide range of severity and symptoms and patients can often find it very distressing, socially disruptive and embarrassing to discuss1. Antimuscarinics are frequently initiated in primary care to treat UI and patients often remain on these long term without regular review for continued need. National Institute for Health Care and Excellence Clinical Guidelines 171 (NICE CG171) recommend annual review in primary care (or every 6 months if over 75 years). They do not give any guidance as to how this should be done. Methods A search was carried out on the medical practices' clinical system using it's reporting function to identify patients prescribed antimuscarinics to treat UI in the last year: Each patient was individually reviewed using their clinical notes; the patient was not contacted as part of the review process. Patients excluded during the review process include: * Treatment less than 1yr (or less than 6 months if over 75yrs) * Attending continence clinic or consultant input * Parkinson's, Multiple Sclerosis or spinal cord injury * Stroke, dementia, Alzheimer's - exclusion depended on severity of condition and if incontinence was associated. * Life circumstance that deemed a change inappropriate The remaining patients were sent a letter asking them to stop their medication. Their medication was removed from their repeat list to ensure the

patient had to make contact with a prescriber/pharmacist before another prescription was issued. Ethics committee approval was not required. Results The search identified 210 patients in this practice currently using antimuscarinics. After the exclusions were applied 70 patients remained and were contacted to ask them to stop their medication. Following a period of eight weeks 51 patients (almost 73%) had remained stopped, 2 had been switched to an alternative antimuscarinic as they had reported that they were still symptomatic on their original medication, 8 patients were unwilling to stop as they felt they still required these and 9 patients tried to stop but found their symptoms returned so were restarted. Patient satisfaction with this review was not analysed. The cost of prescribing these medications on a daily basis for 12 months was worked out for each patient. These were then totalled and for the 51 patients that remained stopped this generated an estimated saving of 14,542 for the practice prescribing budget. Discussion This review confirms the need for regular review of antimuscarinincs to treat UI. Almost 73% of patients asked to stop had remained stopped after an 8 week period which indicates that their symptoms may have resolved and that they no longer required treatment. This supports NICE guidance and the reality that treatment need not always be lifelong. The results were collated following an 8 week period - additional patients may have been restarted after this period. Also the savings generated can only be estimated and rely on the assumption that these patients would continue to take their medication regularly for the next 12 months. This review can be used in primary care to facilitate the reduction in unnecessary prescribing of the antimuscarinics in the treatment of UI benefiting the patient whilst also achieving savings to the primary care prescribing budget.

Title: How appropriate is prescribing for people with dementia in primary care? A cross-sectional analysis

Citation: International Journal of Pharmacy Practice, October 2015, vol./is. 23/(10-11),

Author(s): Barry H.E., Cooper J.A., Ryan C., Passmore A.P., Robinson A.L., Molloy G.J., Darcy C.M., Buchanan H., Hughes C.M.

Abstract: Focal points * Data from the Enhanced Prescribing Database were analysed retrospectively to investigate prescribing trends and appropriateness of prescribing during 2013 for people with dementia in primary care. * One quarter of people with dementia (n = 1,719; 25.2%) received anticholinergic/antimuscarinic drugs and 11.4% of patients (n = 777) were prescribed a benzodiazepine for four weeks or more. * Findings from this study will be considered during the development of an intervention to improve medicines management for people with dementia in primary care. Introduction People with dementia (PWD) have unique medication needs compared with the general older population, which may influence doctors' prescribing behaviour.1 Few studies have specifically focused on prescribing in PWD, particularly community-dwelling patients managed in primary care. The aim of this study is to investigate prescribing trends and the appropriateness of medicines prescribed to PWD in primary care in Northern Ireland during 2013, using the Screening Tool of Older Persons Potentially Inappropriate Prescriptions (STOPP) criteria.2 Methods A retrospective, cross-sectional study is ongoing, using data from the Enhanced Prescribing Database (EPD). Patients were included if they were dispensed a drug for dementia (donepezil, galantamine, rivastigmine, memantine) during the study period 01/01/2013-31/12/2013. These drugs were used as a proxy measure for dementia diagnosis due to lack of clinical information in

the EPD. All patients were required to have three months of lead-in data prior to 01/01/2013 to ascertain long-term use of certain medications. Care home residents or patients who died during the study period were excluded. A subset of the STOPP criteria, comprising 38 indicators which could be used in the absence of clinical information, was applied to the dataset. The prevalence of individual STOP Pcriteria was calculated as a proportion of all eligible persons in the dataset. Data extraction and analysis were performed using Stata SE v13. Ethical approval was obtained for this study. Results Just under 7,000 patients (n = 6,828) were included in the study. More than half were female (n = 4,395; 64.4%), and the mean age was 79.6 [standard deviation (SD) +/- 8.0] years. From the analyses conducted to date, the most common instances of potentially inappropriate prescribing (PIP) were use of first generation antihistamines (n = 635; 9.3%), benzodiazepines prescribed for four weeks or more (n = 777; 11.4%), acetylcholinesterase inhibitors and concurrent treatment with drugs that reduce heart rate (n = 1,276; 18.7%), and anticholinergic/antimuscarinic drugs in patients with dementia (n = 1,719; 25.2%). The drug classes in which therapeutic duplication occurred most frequently were opioid analgesics (n = 346; 5.1%) and benzodiazepines (n = 239; 3.5%). Discussion Analysis conducted to date has revealed a number of instances of PIP amongst the study population during 2013. Further analysis will determine the overall prevalence of PIP within the study population, and logistic regression analysis will be used to explore the association between PIP and polypharmacy, age, and gender. It is anticipated that the findings from this study, together with the findings from an ongoing qualitative study involving PWD, carers, general practitioners and community pharmacists, will help to inform the development of an intervention to improve medicines management for PWD in primary care.

Title: Continuous treatment with antidementia drugs in Germany 2003-2013: A retrospective database analysis

Citation: International Psychogeriatrics, October 2015, vol./is. 27/8(1335-1342)

Author(s): Bohlken J., Weber S., Rapp M.A., Kostev K.

Abstract: Background: Continuous treatment is an important indicator of medication adherence in dementia. However, long-term studies in larger clinical settings are lacking, and little is known about moderating effects of patient and service characteristics. Methods: Data from 12,910 outpatients with dementia (mean age 79.2 years; SD = 7.6 years) treated between January 2003 and December 2013 in Germany were included. Continuous treatment was analysed using Kaplan-Meier curves and log-rank tests. In addition, multivariate Cox regression models were fitted with continuous treatment as dependent variable and the predictors antidementia agent, age, gender, medical comorbidities, physician specialty, and health insurance status. Results: After one year of follow-up, nearly 60% of patients continued drug treatment. Donezepil (HR: 0.88; 95% CI: 0.82-0.95) and memantine (HR: 0.85; 0.79-0.91) patients were less likely to be discontinued treatment as compared to rivastigmine users. Patients were less likely to be discontinued if they were treated by specialist physicians as compared to general practitioners (HR: 0.44; 0.41-0.48). Younger male patients and patients who had private health insurance had a lower discontinuation risk. Regarding comorbidity, patients were more likely to be continuously treated with the index substance if a diagnosis of heart failure or hypertension had been diagnosed at baseline. Conclusions: Our results imply that besides type of antidementia

agent, involvement of a specialist in the complex process of prescribing antidementia drugs can provide meaningful benefits to patients, in terms of more disease-specific and continuous treatment.

Title: The development and testing of the quality use of medications in dementia (QUM-D): A tool for quality prescribing for behavioral and psychological symptoms of dementia (BPSD)

Citation: International Psychogeriatrics, October 2015, vol./is. 27/8(1313-1322)

Author(s): Peisah C., Strukovski J.-A., Wijeratne C., Mulholland R., Luscombe G., Brodaty H.

Abstract: Background: Behavioral and psychological symptoms of dementia (BPSD) are virtually ubiquitous in dementia. Excessive recourse to use of psychotropics which have high risk to benefit ratio remains a global problem. We aimed to identify components of quality prescribing in BPSD to develop a tool for quality prescribing and to test this tool. Methods: We used Delphi methodology to identify elements of quality prescribing in BPSD. The tool was tested by a range of medical and nursing professionals on 48 patients, in inpatient and ambulatory settings in Northern Sydney Local Health District, Australia. Results: Consensual opinion using Delphi method was that quality prescribing in dementia comprised ten factors including failure to use first line non-pharmacological strategies, indication, choice of drug, consent, dosage, mode of administration, titration, polypharmacy, toxicity, and review. These elements formed the quality use of medications in dementia (QUM-D) tool, lower scores of which reflected quality prescribing, with a possible range of scores from 0 to 30. When inter-rater reliability was tested on a subgroup of raters, QUM-D showed high inter-rater reliability. A significant reduction in QUM-D scores was demonstrated from baseline to follow-up, mean difference being 5.3 (SD = 3.8; 95% confidence interval 4.1-6.4; t = 9.5; df = 47; p < 0.001). There was also a significant reduction in score from baseline to follow-up when rated by clinical nurse consultants from a specialized behavior assessment management service (BAMS) (N = 12). Conclusion: The QUM-D is a tool which may help to improve quality prescribing practices in the context of BPSD. In this setting, we consider quality prescribing, and accordingly the obligations of prescribers, to be an inclusive concept rather than just adding to the mantra of "not prescribing."

Title: Drug persistency of cholinesterase inhibitors for patients with dementia of Alzheimer type in Korea

Citation: Archives of Pharmacal Research, October 2015, vol./is. 38/6(1255-1262),

Author(s): Ahn S.-H., Choi N.-K., Kim Y.-J., Seong J.-M., Shin J.-Y., Jung S.-Y., Park B.-J.

Abstract: This study examined 1-year persistency with cholinesterase inhibitors (ChEIs) for the treatment of elderly Alzheimer's dementia (AD) patients in Korea. Korean Health Insurance Review & Assessment Service database from January 2005 to June 2006 was used. Patients aged 65 or older with AD diagnosis who were first prescribed a ChEI were included. The 1-year persistence, persistency rate, and switching patterns during the follow-up period were identified. Mean time to drug discontinuation was analyzed, and persistency rates between different patient factors were compared. The 1-year persistency rate of newly treated 6,461 AD patients was 24.0 %, while 50 % of study patients discontinued treatment by 91 days from initiation. Persistency rates of female patients (22.8 %), patients

in rural areas (12.7 %), and primary care (10.2 %) were relatively low ($p < 0.001$). Persistency rate differed between age groups ($p < 0.001$). Overall proportion of switching was 6.6 %. The 1-year persistency rate of ChEIs for AD patients in Korea did not reach those of previous researches in other countries. Patients less likely to remain on therapy should be especially monitored to optimize treatment persistence.

Title: Pain management: a fundamental component of dementia care.

Citation: Nursing standard (Royal College of Nursing (Great Britain) : 1987), Oct 2015, vol. 30, no. 9, p. 43-50 (October 28, 2015)

Author(s): Regan, Ann, Colling, Jane, Tapley, Michael

Abstract: Pain is a multifaceted experience with physical, psychological, social and spiritual components. Dementia, which is often accompanied by impaired communication, complicates the assessment and treatment of pain. Although older people with dementia share the same age-related pathology as other older people, they do not experience the same access to pain relief as their cognitively-unimpaired counterparts. Tools have been developed to enhance self-reporting of pain by people with dementia and the objective observation of non-verbal signs of pain. The first step, however, is awareness that pain might be present and can be responsible for otherwise unexplained distress and behaviour change. Recognition of pain should trigger the appropriate and timely use of pain assessment tools. Pharmaceutical and non-pharmaceutical measures to relieve pain should be used as appropriate. Evaluation of the efficacy of these methods is needed on an ongoing basis. People living with dementia deserve to be listened to, no matter how they choose to express pain, and to have their pain minimised effectively and efficiently.

Title: Use of Anti-Dementia Drugs in Relation to Change in Cognition, Behavior, and Functioning in Alzheimer's Disease over a Three-Year Period: Kuopio ALSOVA Study.

Citation: Journal of Alzheimer's disease : JAD, Oct 2015, vol. 48, no. 4, p. 1033-1041

Author(s): Törmälehto, Soili M, Martikainen, Janne A, Väätäinen, Saku T, Hallikainen, Ilona T, Hallikainen, Merja, Bell, J Simon, Koivisto, Anne M

Abstract: Alzheimer's disease (AD) is characterized by deterioration in cognition, decline in physical function, and increase in behavioral disturbances. These symptoms are associated with dependence. We investigated the use of anti-dementia drugs in relation to change in cognition, function, and behavior over a 3-year period. Data were collected as part of the prospective follow-up ALSOVA study. All study participants (n = 236) had very mild or mild AD at baseline. All participants and their informal caregivers underwent annual clinical and medication assessments. Repeated measures logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with anti-dementia drug use and disease progression measures over time. The overall prevalence of anti-dementia drug use remained stable (from 89% to 92%) during the follow-up period. The use of memantine and cholinesterase inhibitor-memantine combination treatment increased with disease severity. After adjustment for confounding, a one-point increase in the disease severity scale (CDR-SOB) was associated with 15.6% increased odds of memantine use. A one-point decrease in CERAD Neuropsychological battery (CERAD-NB) total score was

associated with 2.4% increased odds of memantine use. The overall unadjusted rate of switching between anti-dementia drugs was 9.17 (95% CI 7.10 to 11.88) changes per 100 person-years. Nearly 90% of newly diagnosed persons with AD were prescribed anti-dementia drugs. Use of memantine was found to be associated with disease progression. Switching and use of anti-dementia drugs was consistent with Finnish and European clinical practice guidelines for AD.

Title: 1,3,7-Triethyl-substituted xanthines-possess nanomolar affinity for the adenosine A1 receptor.

Citation: Bioorganic & medicinal chemistry, Oct 2015, vol. 23, no. 20, p. 6641-6649

Author(s): Van der Walt, Mietha M, Terre'Blanche, Gisella

Abstract: Adenosine A1 receptors are attracting great interest as drug targets for their role in cognitive deficits. Antagonism of the adenosine A1 receptor may offer therapeutic benefits in complex neurological diseases, such as Alzheimer's and Parkinson's disease. The aim of this study was to discover potential selective adenosine A1 receptor antagonists. Several analogs of 8-(3-phenylpropyl)xanthines (3), 8-(2-phenylethyl)xanthines (4) and 8-(phenoxymethyl)xanthines (5) were synthesized and assessed as antagonists of the adenosine A1 and A2A receptors via radioligand binding assays. The results indicated that the 1,3,7-triethyl-substituted analogs (3d, 4d, and 5d), among each series, displayed the highest affinity for the adenosine A1 receptor with Ki values in the nanomolar range. This ethyl-substitution pattern was previously unknown to enhance adenosine A1 receptor binding affinity. The 1,3,7-triethyl-substituted analogs (3d, 4d, and 5d) behaved as adenosine A1 receptor antagonists in GTP shift assays performed with either rat cortical or whole brain membranes expressing adenosine A1 receptors. Further, in vivo evaluation of 3d showed reversal of adenosine A1 receptor agonist-induced hypolocomotion. In conclusion, the most potent evaluated compound, 8-(3-phenylpropyl)-1,3,7-triethylxanthine (3d), showed both in vitro and in vivo activity, and therefore represent a novel adenosine A1 receptor antagonist that may have potential as a drug candidate for dementia disorders.

Title: Alzheimer's in 3D culture: Challenges and perspectives.

Citation: BioEssays : news and reviews in molecular, cellular and developmental biology, Oct 2015, vol. 37, no. 10, p. 1139-1148 (October 2015)

Author(s): D'Avanzo, Carla, Aronson, Jenna, Kim, Young Hye, Choi, Se Hoon, Tanzi, Rudolph E, Kim, Doo Yeon

Abstract: Alzheimer's disease (AD) is the most common cause of dementia, and there is currently no cure. The "β-amyloid cascade hypothesis" of AD is the basis of current understanding of AD pathogenesis and drug discovery. However, no AD models have fully validated this hypothesis. We recently developed a human stem cell culture model of AD by cultivating genetically modified human neural stem cells in a three-dimensional (3D) cell culture system. These cells were able to recapitulate key events of AD pathology including β-amyloid plaques and neurofibrillary tangles. In this review, we will discuss the progress and current limitations of AD mouse models and human stem cell models as well as explore

the breakthroughs of 3D cell culture systems. We will also share our perspective on the potential of dish models of neurodegenerative diseases for studying pathogenic cascades and therapeutic drug discovery. © 2015 WILEY Periodicals, Inc.

Title: Factors Associated With Hyperphagic Behavior in Patients With Dementia Living at Home.

Citation: Biological research for nursing, Oct 2015, vol. 17, no. 5, p. 567-573 (October 2015)

Author(s): Chi, Lu-Wen, Lin, Shu-Chin, Chang, Shu-Hua, Wu, Hua-Shan

Abstract: To investigate the prevalence and patterns of and factors associated with hyperphagic behavior in Taiwanese patients with dementia living at home. A cross-sectional and correlational design was used. A total of 104 patients with dementia and their primary caregivers were recruited from the geriatric, neurology, and memory clinics of a regional hospital, a medical center and two day-care centers in central Taiwan. The data related to hyperphagic behavior, functional abilities, medical conditions, body weight, and demographic characteristics of patients as well as the demographic characteristics of their primary caregivers were collected between January and May 2013. Based on a strict criterion (a median score of 3 for the hyperphagic subscale), the prevalence of hyperphagia in patients with dementia was 53.8%. Specific hyperphagic patterns exhibited included increased food intake (49% of patients with dementia), hoarding (8.7%), oral exploration (6.8%), and pica (3.9%). Years of education of the patient, the use of antipsychotics in patients, and the age of primary caregivers explained 16.3% of the variance in hyperphagic behavior subscale scores ($F = 6.47$, $p < .001$). For the early identification and treatment of hyperphagic behavior in patients with dementia in home care or in clinic services provided by health professionals, specific attention should be paid to the usual eating behaviors of patients with lower levels of education or who are taking antipsychotic medication or those who have a female primary caregiver. © The Author(s) 2014.

Title: Tablet Splitting of Psychotropic Drugs for Patients With Dementia: A Pharmacoepidemiologic Study in a Brazilian Sample.

Citation: Clinical therapeutics, Oct 2015, vol. 37, no. 10, p. 2332-2338 (October 1, 2015)

Author(s): Mascarenhas Starling, Flávio, Medeiros-Souza, Patrícia, Francisco de Camargos, Einstein, Ferreira, Felipe, Rodrigues Silva, Alessandra, Homem-de-Mello, Maurício

Abstract: The objective of this study was to assess the frequency of tablet splitting of psychotropic drugs in a population of older adults with a diagnosis of dementia. This retrospective, cross-sectional study examined a sample of geriatric outpatients seen at a public center specializing in the care of elderly patients, a referral center for management of dementias in general, especially Alzheimer dementia to identify the frequency of tablet splitting of psychotropic drugs and the factors that may be involved in this practice. Comparison of the presence or absence of tablet splitting in relation to several parameters was assessed by means of P values; between-group differences with an $\alpha < 5\%$ ($P < 0.05$) were deemed significant. The presence of dementia was significantly associated with prescriptions implying to split tablets, which was found in 88 patients with dementia (34.9%) versus 90 patients without dementia (23.7%) ($P = 0.002$). Among the 88 patients with

dementia who split tablets, 64 (72.7%) split tablets of psychotropic drugs. These results indicate the importance of identifying the practice of tablet splitting, particularly when it involves psychotropic drugs, because it entails several factors that can reduce the efficacy of the drug therapy.

Title: Anticholinergic burden in Parkinson's disease inpatients.

Citation: European journal of clinical pharmacology, Oct 2015, vol. 71, no. 10, p. 1271-1277

Author(s): Lertxundi, Unax, Isla, Arantxazu, Solinis, Maria Angeles, Domingo-Echaburu, Saioa, Hernandez, Rafael, Peral-Aguirregoitia, Javier, Medrano, Juan

Abstract: Anticholinergic toxicity can arise as a result of the cumulative burden of multiple medications and metabolites rather than be caused by a single compound. In this sense, prescribing drugs with anticholinergic properties to Parkinson's disease (PD) patients could contribute to aggravate some frequent problems of the disease, like dementia, urinary retention, falls, or constipation, among others. The main purpose of this article is to measure the total anticholinergic burden in a group of PD inpatients. We analyzed information from different administrative Basque Country's healthcare databases using encrypted unique identifiers in order to detect PD patients admitted to public acute care hospital during 2011-2012. Subsequently, anticholinergic burden was measured using Duran et al.'s list. Secondarily, total anticholinergic load was assessed with the Anticholinergic Drug Scale, the Anticholinergic Risk Score, and the Anticholinergic Burden Scale. A logistic regression model was performed to study association of predictive variables with anticholinergic use. A high proportion of PD patients were prescribed anticholinergic drugs, with 53.6 % of admissions receiving at least one drug from Duran et al.'s "low-risk" and 10 % at least "high-risk" drug. Drugs used for non-motor symptoms and other comorbidities other than PD itself contributed significantly to anticholinergic burden, namely antidepressants, antipsychotics, urological drugs, analgesics, and antihistamines, among others. The total number of drugs and cholinesterase inhibitors were independently associated with anticholinergic drug use. Anticholinergic burden in PD patients is significant, and is caused mostly by drugs not used for PD motor symptoms. Polypharmacy and cholinesterase inhibitors were independently associated with anticholinergic drug prescriptions.

Title: Factors that predict cognitive decline in patients with subjective cognitive impairment.

Citation: International psychogeriatrics / IPA, Oct 2015, vol. 27, no. 10, p. 1671-1677

Author(s): Fonseca, Jose Andres Saez, Ducksbury, Rhiannon, Rodda, Joanne, Whitfield, Timothy, Nagaraj, Chitra, Suresh, Kallur, Stevens, Tim, Walker, Zuzana

Abstract: Current evidence supports the concept of a preclinical phase of Alzheimer's disease (AD) where pathological and imaging changes are present in asymptomatic individuals. Subjective cognitive impairment (SCI) may represent the earliest point on the continuum of AD. A better understanding of the baseline characteristics of this group of patients that later decline in cognition will enhance our knowledge of the very early disease processes, facilitate preventive strategies, early diagnosis, timely follow-up and treatment. An observational exploratory study which followed up 62 consecutive patients with SCI presenting to a memory clinic and compared baseline characteristics of SCI patients who

declined cognitively with those who did not. Cognitive decline was defined as a progression to a diagnosis of amnestic mild cognitive impairment (aMCI) or dementia at follow-up. Patients were followed up for a mean of 44 months (range 12-112 months). At the time of follow up, 24% of patients had declined. Patients that declined were significantly older at onset of symptoms and first presentation to memory clinic, and took significantly more medications for physical illnesses. Patients that declined also performed significantly worse on Trail Making Test (TMT) B and Cambridge Cognitive Examination - Revised (CAMCOG-R) at baseline. Survival analysis identified key variables that predicted decline (later age of onset and later age at first assessment). Patients who present with subjective memory complaints and are over the age of 61 years are at high risk of cognitive decline and warrant an in-depth assessment and follow-up.

Title: Identifying phenomenological differences and recovery of cognitive and non-cognitive symptomatology among delirium superimposed upon dementia patients (DsD) versus those without dementia (DaD) in an acute geriatric care setting.

Citation: International psychogeriatrics / IPA, Oct 2015, vol. 27, no. 10, p. 1695-1705

Author(s): Chong, Edward, Tay, Laura, Chong, Mei Sian

Abstract: Phenomenological differences between delirium superimposed on dementia (DsD) versus delirium in the absence of dementia (DaD) remain poorly understood. We aimed to identify phenomenological differences in delirium symptoms (cognitive and non-cognitive) and compare delirium recovery trajectories between DsD and DaD. We conducted a prospective observational study on individuals admitted to the Geriatric Monitoring Unit (GMU), a five-bed unit specializing in managing older adults with delirium, between December 2010 and August 2012 (n = 234; mean age 84.1 ± 7.4). We collected data on demographics, comorbidities, severity of illness, cognitive and functional scores, and number of precipitants. Cognitive status was assessed using locally validated Chinese Mini-Mental State Examination (CMMSE) and delirium severity assessed using Delirium Rating Scale-Revised-98 (DRS-R98). Delirium disease trajectory was plotted over five days. DsD patients had a longer duration of delirium with slower recovery in terms of cognition and delirium severity scores compared with DaD patients (0.33 (0.0-1.00) vs. 1.0 (0.36-2.00) increase in CMMSE per day, $p < 0.001$, and 1.49 ± 1.62 vs. 2.63 ± 2.28 decrease in DRS-R98 severity per day, $p < 0.001$). When cognitive and non-cognitive sub-scores of DRS-R98 were examined separately, we observed steeper recovery in both sub-scores in DaD patients. These findings remained significant after adjusting for significant baseline differences. Our findings of slower cognitive symptom recovery in DsD patients suggest cognitive reserve play a role in delirium syndrome development and recovery. This merits further studies to potentially aid in appropriate discharge planning and to identify potential pharmacological and non-pharmacological cognitive interventions for hospitalized older persons with delirium.

Title: Antihypertensive drug use and risk of cognitive decline in the very old: an observational study - The Newcastle 85+ Study.

Citation: Journal of hypertension, Oct 2015, vol. 33, no. 10, p. 2156-2164 (October 2015)

Author(s): Peters, Ruth, Collerton, Joanna, Granic, Antoneta, Davies, Karen, Kirkwood, Thomas, Jagger, Carol

Abstract: Older adults are a fast growing group in society and are at high risk of hypertension, cognitive decline and dementia. Antihypertensive drugs, particularly calcium channel blockers (CCB), have been associated with a decreased risk of cognitive decline and dementia. We used observational data to examine the association between antihypertensive drug class and change in cognitive function. The Newcastle 85+ Study is a population-based cohort study recruiting individuals aged 85 (born in 1921) via general/family practices in Newcastle/North Tyneside, United Kingdom. Data, including blood pressure, antihypertensive drug use and cognitive function [assessed using the Standardized Mini-Mental State Exam (SMMSE)], were collected at baseline and 3-year follow-up. The study population comprised 238 participants with a diagnosis of hypertension, prescribed antihypertensive drug treatment and with baseline and follow-up SMMSE assessment. There was an association between CCB use and less cognitive decline over 3 years (rate of decline was lower by 1.29 SMMSE points (95% confidence interval 0.16-2.42; P = 0.03) compared with those taking other antihypertensive classes after adjustment for age, sex, years of education, baseline SMMSE score, smoking, BMI, baseline blood pressure, and incident cerebrovascular event. This finding was even stronger in the cognitively intact (SMMSE >24), wherein rate of cognitive decline was lower by 1.33 SMMSE points (95% confidence interval 0.30-2.37; P = 0.01), but was not seen for other antihypertensive classes. Findings provide support for an association between CCB use and a lower rate of cognitive decline in very old adults with hypertension.

Title: Plant alkaloids as drug leads for Alzheimer's disease.

Citation: Neurochemistry international, Oct 2015, vol. 89, p. 260-270 (October 2015)

Author(s): Ng, Yu Pong, Or, Terry Cho Tsun, Ip, Nancy Y

Abstract: Alzheimer's disease (AD) is a neurodegenerative illness associated with dementia and is most prevalent among the elderly population. Current medications can only treat symptoms. Alkaloids are structurally diverse and have been an important source of therapeutics for various brain disorders. Two US Food and Drug Administration (FDA)-approved acetylcholinesterase inhibitors for AD, galantamine and rivastigmine, are in fact alkaloids. In addition, clinical trials of four other extensively studied alkaloids-huperzine A, caffeine, nicotine, and indomethacin-have been conducted but do not convincingly demonstrate their clinical efficacy for AD. Interestingly, rhynchophylline, a known neuroprotective alkaloid, was recently discovered by in silico screening as an inhibitor of EphA4, a novel target for AD. Here, we review the pathophysiological mechanisms underlying AD, current treatment strategies, and therapeutic potential of several selected plant alkaloids in AD, highlighting their various drug targets and the key supportive preclinical and clinical studies. Future research should include more rigorous clinical studies of the most promising alkaloids, the further development of recently discovered candidate alkaloids, and the continual search for new alkaloids for relevant drug targets. It remains promising that an alkaloid drug candidate could significantly affect the progression of AD in addition to providing symptomatic relief.

Title: Evolving trends in cerebral amyloid angiopathy research themes: Insights from medical subject heading analysis.

Citation: Journal of the Neurological Sciences, Oct 2015, vol. 357, no. 1-2, p. 341-342

Author(s): Charidimou, Andreas, Song, Min

Abstract: The letter discusses about the evolving trends in cerebral amyloid angiopathy research themes. The author systematically harvested CAA-related publications (without language restriction) and their associated MeSH terms from the National Center for Biotechnology Information's PubMed using a combination of search terms: “amyloid angiopathy” or “congophilic angiopathy” or “dyshoric angiopathy” or “dysphoric angiopathy”. The search covered the period from 1950 to 2015. A total of 2153 unique papers directly or indirectly related to CAA were published from 1990 through 2014 in PubMed. Using MeSHbased categories we have identified and explored the following major clinically-relevant themes in the field of CAA research across all articles1): antithrombotic drugs, MRI, neuropathological aspects (including capillary CAA and tangles), cognitive impairment/dementia, intracerebral haemorrhage, subarachnoid haemorrhage/cortical superficial siderosis and other themes (including Alzheimer disease, hypertension and CAA-related ischaemic features). (PsycINFO Database Record (c) 2015 APA, all rights reserved)

Title: Modeling als and ftd with ipsc-derived neurons.

Citation: Brain Research, Oct 2015, (Oct 14, 2015), 0006-8993 (Oct 14, 2015)

Author(s): Lee, Sebum, Huang, Eric J.

Abstract: Recent advances in genetics and neuropathology support the idea that amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTD) are two ends of a disease spectrum. Although several animal models have been developed to investigate the pathogenesis and disease progression in ALS and FTD, there are significant limitations that hamper our ability to connect these models with the neurodegenerative processes in human diseases. With the technical breakthrough in reprogramming biology, it is now possible to generate patient-specific induced pluripotent stem cells (iPSCs) and disease-relevant neuron subtypes. This review provides a comprehensive summary of studies that use iPSC-derived neurons to model ALS and FTD. We discuss the unique capabilities of iPSC-derived neurons that capture some key features of ALS and FTD, and underscore their potential roles in drug discovery. There are, however, several critical caveats that require improvements before iPSC-derived neurons can become highly effective disease models. This article is part of a Special Issue entitled SI: Exploiting human neurons. (PsycINFO Database Record (c) 2015 APA, all rights reserved)(journal abstract)

Title: Perk inhibition prevents tau-mediated neurodegeneration in a mouse model of frontotemporal dementia.

Citation: Acta Neuropathologica, Oct 2015, (Oct 8, 2015), 0001-6322 (Oct 8, 2015)

Author(s): Radford, Helois, Moreno, Julie A., Verity, Nicholas, Halliday, Mark, Mallucci, Giovanna R.

Abstract: The PERK-eIF2α branch of the Unfolded Protein Response (UPR) mediates the transient shutdown of translation in response to rising levels of misfolded proteins in the endoplasmic reticulum. PERK and eIF2α activation are increasingly recognised in postmortem analyses of patients with neurodegenerative disorders, including Alzheimer's disease, the tauopathies and prion disorders. These are all characterised by the accumulation of misfolded disease-specific proteins in the brain in association with specific patterns of neuronal loss, but the role of UPR activation in their pathogenesis is unclear. In prion-diseased mice, overactivation of PERK-P/eIF2α-P signalling results in the sustained reduction in global protein synthesis, leading to synaptic failure, neuronal loss and clinical disease. Critically, restoring vital neuronal protein synthesis rates by inhibiting the PERK-eIF2α pathway, both genetically and pharmacologically, prevents prion neurodegeneration downstream of misfolded prion protein accumulation. Here we show that PERK-eIF2α-mediated translational failure is a key process leading to neuronal loss in a mouse model of frontotemporal dementia, where the misfolded protein is a form of mutant tau. rTg4510 mice, which overexpress the P301L tau mutation, show dysregulated PERK signalling and sustained repression of protein synthesis by 6 months of age, associated with onset of neurodegeneration. Treatment with the PERK inhibitor, GSK2606414, from this time point in mutant tau-expressing mice restores protein synthesis rates, protecting against further neuronal loss, reducing brain atrophy and abrogating the appearance of clinical signs. Further, we show that PERK-eIF2α activation also contributes to the pathological phosphorylation of tau in rTg4510 mice, and that levels of phospho-tau are lowered by PERK inhibitor treatment, providing a second mechanism of protection. The data support UPR-mediated translational failure as a generic pathogenic mechanism in protein-misfolding disorders, including tauopathies, that can be successfully targeted for prevention of neurodegeneration. (PsycINFO Database Record (c) 2015 APA, all rights reserved)(journal abstract)

Title: Possible role of p-glycoprotein in the neuroprotective mechanism of berberine in intracerebroventricular streptozotocin-induced cognitive dysfunction.

Citation: Psychopharmacology, Oct 2015, (Oct 8, 2015), 0033-3158 (Oct 8, 2015)

Author(s): Kumar, Anil, Ekavali, Mishra, Jitendriya, Chopra, Kanwaljit, Dhull, Dinesh K.

Abstract: Rationale: The therapeutic potential of berberine has been well documented in various neurological problems. However, the neurological mechanism of berberine remains untapped in the light of its P-glycoprotein (P-gp)-mediated gut efflux properties responsible for reduced bioavailability. Verapamil, a well known L-type calcium channel blocker, has additional inhibitory activity against P-gp efflux pump. Thus, there is a strong scientific rationale to explore the interaction of berberine with verapamil as a possible neuroprotective strategy.Objective: The present study was designed to evaluate the effect of berberine, verapamil, and their combination on behavioral alterations, oxidative stress, mitochondrial dysfunction, neuroinflammation, and histopathological modifications in intracerebroventricular streptozocin (ICV-STZ)-induced sporadic dementia of Alzheimer's type in rats.Methods: Single bilateral ICV-STZ (3 mg/kg) administration was used as an experimental model of sporadic dementia of Alzheimer's type.Results: Berberine (25, 50,

and 100 mg/kg, oral gavage) or verapamil (2.5 and 5 mg/kg, intraperitoneally) were used as treatment drugs, and memantine (5 mg/kg, intraperitoneally) was used as a standard. Berberine and verapamil significantly attenuated behavioral, biochemical, cellular, and histological alterations, suggesting their neuroprotective potential. Further, treatment of berberine (25 and 50 mg/kg) with verapamil (2.5 and 5.0 mg/kg) combinations respectively significantly potentiated their neuroprotective effect which was significant as compared to their effect per se in ICV-STZ-treated animals.Conclusion: The augmentative outcome of verapamil on the neuroprotective effect of berberine can be speculated due to the inhibition of P-gp efflux mechanism and the prevention of calcium homeostasis alteration. Additionally, anti-inflammatory and antioxidant effects of both berberine and verapamil could also contribute in their protective effect. (journal abstract)

Title: Pharmacotherapy of dementia in germany: Results from a nationwide claims database.

Citation: European Neuropsychopharmacology, Oct 2015, (Oct 3, 2015), 0924-977X (Oct 3, 2015)

Author(s): Bohlken, Jens, Schulz, Mandy, Rapp, Michael A., Bätzing-Feigenbaum, Jörg

Abstract: In 2011, about 1.1–1.4 million patients with dementia were living in Germany, a number expected to rise to three million by 2050. Dementia poses a major challenge to the healthcare system and neuropharmacological service provision. The aim of this study was to determine prescription rates for anti-dementia drugs as well as for neuroleptics, sedative-hypnotics and antidepressants in dementia using the complete nationwide outpatient claims data pertaining to the services of statutory health insurance. We controlled for gender, age, dementia diagnosis, physician specialty (general practitioner GP versus neuropsychiatry specialist physician NPSP), and rural and urban living area. In about one million prevalent dementia patients (N=1,014,710) in 2011, the prescription prevalence rate of anti-dementia drugs was 24.6%; it varied with gender, age, and diagnosis (highest in Alzheimer's disease; 42%), and was higher in patients treated by NPSPs (48% vs. 25% in GPs). At the same time, we found an alarmingly high rate of treatment with neuroleptics in dementia patients (35%), with an only slightly decreased risk in patients treated exclusively by NPSPs (OR=0.86). We found marginal differences between rural and urban areas. Our results show that the majority of anti-dementia drug prescriptions appear guideline-oriented, yet prescription rates are overall comparatively low. On the other hand, neuroleptic drugs, which are associated with excess morbidity and mortality in dementia, were prescribed very frequently, suggesting excess use given current guidelines. We therefore suggest that guideline implementation measures and increasing quality control procedures are needed with respect to the pharmacotherapy of this vulnerable population. (journal abstract)

Title: Rivastigmine tartrate (generic) EXELON (BRAND).

Citation: , 02 October 2015, vol./is. 26/(1-2), 10685308

Abstract: The article offers information on the rivastigmine tartrate, a reversible cholinesterase inhibitor. Topics discussed include its side effects, dosage, and indication for treatment of dementia of the Alzheimer's type and dementia associated with Parkinson's disease. It also mentioned its interaction with other medications, identification, and storage.

Title: Research Session 2: Primary care and community practice.

Citation: , 02 October 2015, vol./is. 23/(9-), 09617671

Abstract: The article presents abstracts on pharmacy-related topics in Great Britain which include pharmacists' access to medical records, appropriate prescribing for people with dementia in primary care, and pharmacy emergency repeat medication supply service.

Title: Drugs used to treat dementia can be deadly, report asserts.

Citation: , 01 October 2015, vol./is. 36/10(6-), 10483314

Author(s): Marselas, Kimberly

Abstract: The article discusses a study published in the journal "JAMA Psychiatry" on the increased risk of patient death associated with antipsychotic agents used to control symptoms of dementia including haloperidol, risperidone, and olanzapine.

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- **Age and Ageing**
- **Journal of the American Geriatrics Society**

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Alzheimer's and Dementia

Vol. 11; Iss. 10; October 2015

http://www.alzheimersanddementia.com/current

Dementia: The International Journal of Social Research and Practice

Vol. 14, iss.4; November 2015

http://dem.sagepub.com/content/14/6.toc

Age and Ageing

Vol. 44, iss. 6, November 2015

http://ageing.oxfordjournals.org/content/current

Journal of the American Geriatrics Society

Vol. 63, Iss. 10; October 2015

http://onlinelibrary.wiley.com/doi/10.1111/jgs.2015.63.issue-10/issuetoc

John's Campaign

http://www.johnscampaign.org.uk/

Suffolk Family Carers AGM

Wednesday, 25/11/2015

Nicci Gerrard will be giving the keynote speech at Suffolk Family Carers AGM.

John's Campaign in Northern Ireland

Tuesday, 24/11/2015

Nicci and Julia visit Northern Ireland to introduce John's Campaign

Patient Opinion - First Decade

Thursday, 19/11/2015

Our partners at Patient Opinion are celebrating ten years of helping patients and their families make their voices heard. We are looking forward to attending their celebrations.

Nursing Times Awards

Thursday, 12/11/2015

We are supporting the dementia team from Imperial Healthcare who have been shortlisted for one of these prestigious awards.

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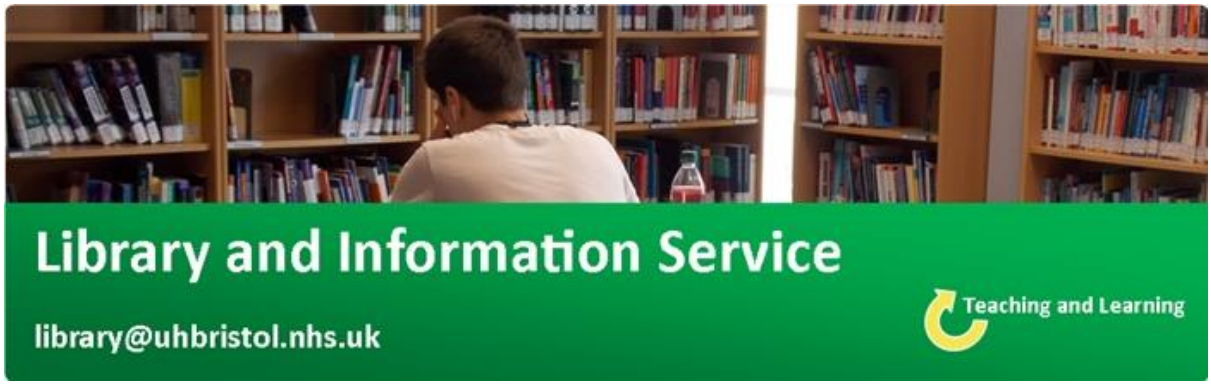

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