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"HE WAS LIKE A ZOMBIE": OFF-LABEL PRESCRIPTION OF ANTIPSYCHOTIC DRUGS IN DEMENTIA

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Abstract: This paper explores the legal position of the off-label prescription of antipsychotic medications to people with dementia who experience behavioural and psychological symptoms of dementia (BPSD). Dementia is a challenging illness, and BPSD can be very difficult for carers to manage, with evidence that this contributes to carer strain and can result in the early institutionalisation of people with dementia. As a result, the prescription of antipsychotic and other neuroleptic medications to treat BPSD has become commonplace, in spite of these drugs being untested and unlicensed for use to treat older people with dementia. In recent years, it has become apparent through clinical trials that antipsychotic drugs increase the risk of cerebrovascular accident (stroke) and death in people with dementia. In addition, these types of medication also have other risk factors for people with dementia, including over-sedation and worsening of cognitive function. Drawing on recent questionnaire (n=185), focus group (n=15) and interview (n=11) data with carers of people with dementia, this paper explores the law relating to off-label prescription, and the applicability of medical negligence law to cases where adverse events follow the use of antipsychotic medication. It is argued that the practice of off-label prescribing requires regulatory intervention in order to protect vulnerable patients.

Keywords: Off-label; antipsychotics; dementia; Alzheimer's disease; medical negligence; tort

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Dementia is an extremely common disease, which predominantly affects older people. There are an estimated number of 25 million people with dementia worldwide.[1] Research commissioned by the Alzheimer's Society,[2] which has been accepted by the National Audit Office (NAO) as providing the most accurate figures available,[3] estimates that there were 683,597 people living with dementia in the UK in 2007. This figure includes at least 15,034 people with younger onset dementia (dementia diagnosed before the age of 65), and total numbers are estimated to increase to over 1 million by

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[1] CP Ferri, M Prince, C Brayne et al. Alzheimer's Disease International 'Global prevalence of dementia: a Delphi consensus study' (2005) 366 *Lancet* 2112-2117.

[2] M Knapp, M Prince, E Albanese, S Banerjee, S Dhanasiri, JL Fernandez, C Ferri , P McCrone, T Snell, R Stewart *Dementia UK: A Report to the Alzheimer's Society on the prevalence and economic cost of dementia in the UK* (Alzheimer's Society, London, 2007).

[3] National Audit Office *Improving services and support for people with dementia: Report by the comptroller and auditor general* HC 604 (2007).

2025, given trends towards an ageing population.[4] Many people with dementia experience one or more of the behavioural and psychological symptoms of dementia (BPSD) which can include a variety of problems including delusions, hallucinations, depression, anxiety, sleeplessness, wandering, agitation and physical aggression.[5] It has been suggested that BPSD can occur in up to 90% of people with Alzheimer's disease, which is the most common variant of dementia.[6] BPSD contribute significantly to carer strain,[7] and can result in the hospitalisation and/or early institutionalisation of people with dementia.[8] Historically, these symptoms of dementia were most commonly treated with antipsychotic medications.[9]

In a recent report for the British Government investigating the use of antipsychotic medication for people with dementia in the NHS in England, Professor Sube Banerjee reported that antipsychotics were over-prescribed in dementia, and that there were significant risks of harm to people with dementia from the prescription of these medications.[10] It is estimated that up to 180,000 people with dementia are treated with antipsychotic medication in England each year, at a cost of £90 million.[11] As such, the prescription of antipsychotic medication forms part of the treatment of a significant proportion (up to 25%) of people with dementia each year, at significant cost to the NHS. Only one atypical antipsychotic medication, Risperidone, is currently licensed for use in people with dementia for treating persistent aggression in "patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and where there is a risk of harm to self or others".[12] It is only licensed for use for short periods (up to 6 weeks). In contrast to this licensed use, a wide variety of antipsychotic medications are prescribed 'off-label'. Off-label prescribing is the term given to the act of prescribing a medication for the treatment of either a medical condition or patient group that is not included on the marketing authorisation from the Medical and Healthcare products Regulatory Agency (MHRA).[13] Off-label prescribing is both legal and commonplace, falling as it does within the professional judgment of the prescribing medical professional. Off-label prescribing must be contrasted with 'unlicensed' drug use, which has been defined as "all uses of a

[4] Knapp et al (n 2). Prevalence rates for dementia increase with age: 40-64 years: 1 in 1400, 65-69 years: 1 in 100, 70 – 79 years, 1 in 25, 80+ years 1 in 6. (Alzheimer's Society website: http://www.alzheimers.org.uk/site/scripts/documents_info.php?categoryID=200167&documentID=412, accessed August 2010)

[5] National Collaborating Centre for Mental Health *Dementia: a NICE-SCIE Guideline on supporting people with dementia and their carers in health and social care*. National Clinical Practice Guideline no. 42. (Leicester: British Psychological Society 2011). (NICE *Dementia*).

[6] P.H. Robert et al. 'Grouping for behavioral and psychological symptoms in dementia: clinical and biological aspects' Consensus paper of the European Alzheimer disease consortium. (2005) 20 European Psychiatry 490–496.

[7] C Donaldson, N Tarrier and A Burns 'The impact of the symptoms of dementia on caregivers' (1997) 170 The British Journal of Psychiatry 62–68.

[8] S Banerjee, J Murray, B Foley, L Atkins, J Schneider, A Mann 'Predictors of institutionalisation in people with dementia' (2003) 74 Journal of Neurology, Neurosurgery & Psychiatry 1315-1316.

[9] S Banerjee *The use of antipsychotic medication for people with dementia: Time for action* (London, Department of Health 2009).

[10] Banerjee, (n 9).

[11] Alzheimer's Society website 'Facts on Antipsychotic Drugs' available at http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=535&pageNumber=3, accessed on 01 March 2012; Banerjee, (n 9) 51.

[12] NICE *Dementia* (n 5).

[13] A Neubert, M Felisi, A Bonifazi, C Manfredi, ICK Wong and A Ceci 'Off-label and unlicensed use of medicines for children'(2009) 11 Pharmaceuticals Policy and Law 41–49.

drug which has never received a European Marketing Authorisation as medicinal for human use in either adults or children."[14]

There are a number of specific risks of harm associated with the use of antipsychotic medications to treat people with dementia. These include an increased risk of cerebrovascular accident (stroke), and an increased risk of death.[15] These risks were quantified in Banerjee's report as equating to 1,620 additional cerebrovascular accidents per annum in people with dementia, and 1,800 deaths, based on an estimate of 180,000 people per annum being treated with antipsychotics.[16] Of most concern is the increased mortality risk, which Banerjee estimates based on short term (6-12 week) prescription. Where longer term treatment is used, the mortality risk is even higher: "longer-term treatment may result in up to 167 additional deaths among 1,000 people with dementia treated with antipsychotics over a two-year period".[17] This amounts to a 16.7% mortality rate for long-term prescription of antipsychotic medications to people with dementia; an extraordinarily high incidence of such a severe adverse effect of medication.

Such a high manifestation of adverse effects of medical practice raises important legal questions that must be addressed, and are the focus of this paper. The first question that arises is how it is possible for medications that have such high risks attached to them to be prescribed 'off-label' to a vulnerable population such as people with dementia. Part 1 provides an overview of the operation of the regulatory framework surrounding prescription medication, including statutory regulation and the 'soft law' approaches that supplement it. We interrogate the legality of off-label prescription of medications, highlighting key flaws in the regulation of this aspect of medical practice. In Part 2, we turn to some of the empirical findings from the Duties to Care[18] dementia project and the Dementia Talking project.[19] Drawing on carers responses to a questionnaire (n=185), and qualitative comments from participants in focus groups (n=15) and interviews (n=11), we demonstrate the ways that the potential harm caused by the off-label prescription of antipsychotic medication are experienced by carers of people with dementia, highlighting the limitations of the current law in this area. In Part 3 we build on this analysis to emphasise the limitations of the current regulatory regimes of medicines regulation and medical negligence in respect of off-label prescribing. We explore whether there are currently appropriate legal remedies available to people with dementia who suffer harm through the use of off-label prescriptions of antipsychotic medication. Finally in Part 4, we present an argument for reform of the legal frameworks surrounding off-label prescribing of antipsychotic medication to control the non-cognitive symptoms of dementia.

I: OFF-LABEL PRESCRIBING

[14] *ibid*, 47.
[15] LS Schneider, KS Dagerman and P Insel 'Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials' (2005) 294 Journal of the American Medical Association 1934-1943.
[16] Banerjee, (n 9) 28.
[17] ibid, 27.
[18] R Harding and E Peel, 'Duties to Care: A socio-legal study of caring for people with dementia', funded by the British Academy Small Grant SG1000017 (2010-2012).
[19] E Peel, 'Dementia Talking: Care, conversation and communication', funded by the British Academy Mid-Career Fellowship (2011-2012).

A: Licensing of Medicines

In the UK, prior to being made available for public use, all medicinal products must have a marketing authorisation from the MHRA.[20] In order to grant a licence for a medication, the MHRA must satisfy itself that the medication is relatively safe, effective and of consistent quality.[21] The aim of having a licensing system for medications is to protect public health by ensuring that prior to being made available to patients, all medications must be tested through clinical trials to ensure that they are effective, and that the risk profile of side effects is not so great as to outweigh any benefit from them.[22] Marketing authorisations are time-limited, and manufacturers must apply for a renewal of the product license at least every five years, thus giving an opportunity to present data from additional trials, and perhaps to extend the licensed use of particular medications.[23] As part of the licensing process, manufacturers must submit full information about research that has taken place into the medication, the results of trials and any adverse reactions. They must also provide information about how the medication is made, the quality control processes the manufacturer uses, and information about how the medication will be marketed including any patient information leaflets that will be supplied with the product.[24]

The legislative framework for medication classifies medicines into three categories: 1) prescription only medications;[25] 2) medications that can be supplied by a pharmacist[26] without prescription; and 3) general sale list[27] medicines that do not need to be sold by a pharmacist. Medications that are likely to present a direct or indirect danger to human health; are frequently or widely used incorrectly; contain substances which require further investigation; or are normally prescribed intravenously are usually prescription only.[28] Additionally, where a medicine is likely to present a substantial risk of addiction, or is likely to be abused, it will be a prescription only medication.[29] Where a medicine is prescription-only, it can only be supplied following prescription by an

[20] Medicines Act 1968, s. 7. Where the medication is for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, the marketing authorisation will be granted by the European Medicines Agency (EMEA) which was established by Regulation (EC) No. 726/2004 OJ L 136, 30.4.2004, and is governed by Council Directive 2001/83/EEC on the Community Code Relating to Medicinal Products for Human Use OJ – 311, 28.11.2004 (as amended). The MHRA is a national competent body under the EMEA,

[21] Medicines Act 1968, s. 19.

[22] Medicines and Healthcare products Regulatory Agency website, available at: http://www.mhra.gov.uk/Aboutus/Whoweare/index.htm accessed on 16 March 2012.

[23] ibid, at http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/index.htm#11 accessed on 16 March 2012.

[24] MHRA *Medicines and Medical Devices Regulation: What you need to know* (2008) available at http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con2031677.pdf, accessed on 16 March 2012.

[25] Medicines Act 1968, s. 58.

[26] Medicines Act 1968, s. 52.

[27] Medicines Act 1968, s. 51.

[28] Medicines Act 1968, s. 58A(2).

[29] Medicines Act 1968, s. 58A(3).

appropriate practitioner.[30] Once a medicine has a marketing authorisation, it can be freely prescribed by an appropriate practitioner[31] and subsequently supplied by a pharmacist.

There is also a complex array of post-license regulation: manufacturers must provide specific information on the labelling and in the patient information leaflet supplied with medicines.[32] There are restrictions concerning the marketing of products, and in the UK prescription-only medications cannot be directly marketed to the general public.[33] Marketing medications to healthcare providers is authorised, and pharmaceutical companies go to great lengths to sell their products to healthcare professionals, including funding continuing professional development for medical professionals.[34] There are also post-marketing processes for the identification of adverse drug reactions, and the reporting of these to the MHRA. In particular, there is a 'Black Triangle' scheme for new drugs, which are monitored closely for the first two years of their license, during which time there is a requirement to notify all adverse reactions. For other drugs, only serious suspected reactions must be notified, though all reactions can be notified either by health professionals or members of the public through the 'Yellow Card Scheme'.[35] There is, however, no restriction placed on the *uses* of medicines which have a marketing authorisation through the current regulatory framework. Prescription only medications can therefore be prescribed for conditions or patient groups other than those for which they were designed, tested and licensed. Uses of medicines other than those on the marketing authorisation are often referred to as 'off-label' prescription.

The practice of off-label prescription is commonplace, and is an important tool for medical professionals. This is particularly true in paediatric practice, where only very few medicines have specific licenses for use with children, in part due to the legal and ethical difficulties associated with testing drugs on minors. As such, off-label (and unlicensed) medications are regularly prescribed to children in hospital settings. For example, research has suggested that off-label prescription accounts for over 70% of medication used to treat children in an intensive care unit,[36] and over a third of prescribing on in-patient children's wards in Europe.[37] Similarly, most medications are tested on, and therefore licensed for use, in adult populations under the age of 70. Despite the commonplace nature of off-label prescription, however, the regulation of this practice is felt to be unsatisfactory both for patients and doctors.[38] A key reason why the current framework is felt to be unsatisfactory is that in the absence of specific regulation relating to off-label uses, responsibility for harm ultimately lies with the individual prescriber, subject to the common law rules of medical

[30] Medicines Act 1968, s. 58.
[31] ibid, s. 58.
[32] Medicines (Labelling) Regulations 1976 SI 1976/1726, as amended; Medicines (Leaflets) Regulations 1977 SI 1977/1055, as amended.
[33] Medicines (Advertising) Regulations 1994 SI 1994/1932, as amended.
[34] Royal College of Physicians *Innovating for Health: Patients, the Pharmaceutical Industry and the NHS* (RCP, London 2009).
[35] MHRA Yellow Card Scheme available at: http://yellowcard.mhra.gov.uk/ accessed on 16 March 2012.
[36] GW 't Jong, AG Vulto, M de Hoog, et al. 'Survey of the use of off-label and unlicensed drugs in a Dutch children's hospital' (2001) 108 Pediatrics 1089–1093.
[37] S Conroy, et al. 'Survey of unlicensed and off label drug use in paediatric wards in European countries' (2000) 320 BMJ 79–82.
[38] P Hill, 'Off licence and off label prescribing in children: litigation fears for physicians' (2005) 90 (Suppl I) Archives of Disease in Childhood i17-i18.

negligence.[39] The regulation of off-label prescription of medicines therefore falls at the intersection of two legal regimes. The first is a complex statutory regime, concerned with determining the safety of drugs prior to their use in practice; the second is the common law regime governing the tort of negligence. We now turn to explore how the prescription of antipsychotic medication for treating the behavioural and psychological symptoms of dementia fits within this dual regime.

B: Antipsychotics and Dementia

Antipsychotic medications have been used for decades to sedate, calm and control people with dementia.[40] These drugs are used to treat BPSD, sometimes also referred to as 'non-cognitive' symptoms. Antipsychotics do not slow the progression of the disease, nor remove the cause of, or trigger for BPSD. Often (but by no means always), BPSD are as a result of difficulties in communication and can be the result of a complex array of factors associated with both the progression of dementia, and a range of other "psychosocial factors, which interact with biological factors and influence greatly the presenting picture."[41]

As we mentioned earlier, at present only one antipsychotic medication (Risperidone) has a marketing authorisation from the MHRA that includes the treatment of BPSD. This licence followed a period of over six years when Risperidone (along with another atypical antipsychotic, Olanzapine) was explicitly contra-indicated for people with dementia, following guidance issued by the Committee on the Safety of Medicines (CSM) that the risk of stroke outweighed any modest benefits associated with the use of these drugs in controlling BPSD.[42] The limitations on the prescribing period are particularly important, as this seems to be out of line with current practices in relation to the prescription of antipsychotic medication to people with dementia in the NHS in England. Rather than short term, acute treatment, it is thought that antipsychotic use in people with dementia is more likely to be long term and rarely reviewed.[43]

Initially, the increased mortality and CVAE risks were thought to be confined to the class of antipsychotic medications known as 'atypical antipsychotics'. As a result of the warnings, it was noted that there was an increase in prescribing 'typical antipsychotics' to elderly patients with dementia.[44] Typical antipsychotics have a greater chance of negative side effects including over-sedation, accelerated cognitive decline, extrapyramidal side-effects and tardive dyskinesia.[45] Atypical antipsychotics have a slightly different side-effect profile, including: weight gain, disruption of blood glucose control, hyperlipidaemia and cerebrovascular adverse events, as well as sedation and

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[39] We return to the application of the tort of negligence in part 3 below.
[40] L Parnetti , S Amici, A Lanari, V Gallai 'Pharmacological treatment of non-cognitive disturbances in dementia disorders' (2001) 122(16) Mechanisms of Ageing and Development 2063–2069.
[41] NICE *Dementia* (n 5), 220.
[42] Ibid, 237.
[43] C Ballard, M L Hanney, M Theodoulou, S Douglas, R McShane, K Kossakowski, R Gill, E Juszczak, L Yu, R Jacoby 'The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial' (2009) 8 Lancet Neurology 151–57.
[44] Royal College of Psychiatrists Faculty for the Psychiatry of Old Age 'Atypical antipsychotics and behavioural and psychological symptoms of dementia: Prescribing update for old age psychiatrists' (2004) available at: http://www.rcpsych.ac.uk/pdf/bpsd.pdf accessed on 02/03/2012. (RCPsych 2004)
[45] Ibid, 3.

extrapyramidal side-effects at higher doses.[46] Following this, the Committee for Medicinal Products for Human Use (CMHP) issued a report[47] declaring that the risks associated with atypical antipsychotics were similarly applicable to the older class of antipsychotic medications known as 'typical antipsychotics'. On the basis of this report, it is now considered that the increased risks of stroke and death are a class effect relating to all antipsychotics when prescribed to elderly people with dementia.

Reliable statistics relating to the prescription of antipsychotics to people with dementia are currently unavailable, as data on prescribing practices has not historically been recorded. An audit of prescribing practices in the NHS has recently been carried out, and suggests a reduction in the prescription of these medications in general practice over the last five years, though no figures are available for specialist prescription (e.g. by psychiatrists) or prescriptions in general hospitals.[48] Banerjee suggested that between 30 and 50 per cent of people with dementia in residential and nursing homes may be prescribed antipsychotic medication, and that:

> From the evidence available, it is clear that there are particular risks associated with the use of antipsychotics in people with dementia. Antipsychotics appear to be used all too often, in secondary as well as primary care, as a formulaic first-line response to any behavioural difficulty in dementia rather than as a considered second-line treatment when other approaches have failed. The data suggest that antipsychotics are used too often in dementia.[49]

Given the risks of harm associated with the use of antipsychotics that have been identified in clinical research and practice, this level of off-label use is clearly unacceptable, particularly as the efficacy of antipsychotic medication to treat BPSD is not proven.[50] The lack of evidence of efficacy may account for the limited number of antipsychotic medications that have, to date, been licensed for use in older people with dementia. There are significant costs to pharmaceutical companies of gathering the clinical trial evidence for efficacy and safety that would be required to obtain an MHRA license for treating BPSD with antipsychotic medication. Given the "high placebo response rates"[51] reported for the use of medication to control BPSD, and the extensive off-label prescription,[52] it is little wonder that there is limited will from the pharmaceutical industry to apply for licenses for these medications.

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[46] Ibid.
[47] CMHP Assessment Report on Conventional Antipsychotics (Procedure under Article 5(3) of Regulation (EC) No 726/2004.
[48] 'National Dementia and Antipsychotic Prescribing Audit' available at http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/national-dementia-and-antipsychotic-prescribing-audit accessed on 24 July 2012.
[49] Banerjee (n 9), 30.
[50] T Declercq, M Petrovic, R Vander Stichele, AIM De Sutter, ML van Driel, T Christiaens. 'Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and neuropsychiatric symptoms in elderly patients with dementia' Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD007726.
[51] ibid.
[52] The Alzheimer's society estimate the per annum cost to the UK of antipsychotic medication in dementia is approximately £90 million. Alzheimer's Society website 'Facts on Antipsychotic Drugs' available at http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=535&pageNumber=3, accessed on 01 March 2012.

In addition to the clinical harms outlined above, carers of people with dementia report a range of other, perhaps less drastic, but often equally upsetting harms associated with the off-label use of antipsychotic medication. In the next part, we turn to the findings from recent empirical research exploring the experiences that carers of people with dementia have of the regulation of health and social care.

II: CARERS' EXPERIENCE OF ANTIPSYCHOTIC MEDICATION

A: Method and Participant Demographics

The empirical data drawn on here were generated through a tripartite data collection process exploring carers' experiences of access to, and the regulation of, health and social care support services for people with dementia. The findings are drawn from two inter-linked research projects, which included a multi-method online and paper questionnaire (n=185), followed up with four focus groups (n=15) and eleven in-depth interviews.[53] Survey respondents were recruited through strategic opportunistic and snowball sampling via relevant charitable/third sector organizations including carers groups and support services. Paper recruitment packs were posted to a total of 461 dementia and/or care-focused support groups run by the Alzheimer's Society and the Princess Royal Trust for Carers. These paper packs were followed up a fortnight later with email reminders. Recruitment emails were sent to an additional 13 dementia-related organisations, and recruitment details were posted on four online discussion forums. The questionnaire was live for a period of four months, between February and May 2011. Carers could either complete the questionnaire online (n=154) or contact the research team for a postal questionnaire pack (n=31).

Given the varied nature of the recruitment strategy, and our reliance on the goodwill of 'gatekeepers', it is difficult to assess the response rate, though a basic calculation of number of completed questionnaires (185)/number of recruitment messages, emails and postal contacts (939), suggests a response rate of just under 20% overall. Participants in the focus groups and interviews were predominantly recruited from within the questionnaire responses. As this research is based on an opt-in, convenience sample, there are limited claims that can be made about the generalizability of the findings, though we do note where our findings are similar to those in previous research. Quantitative results from the survey were analysed using SPSS to find frequencies and differences between groups of respondents. Qualitative results from the focus groups and interviews were independently coded by the research team, using both deductive and inductive codes. Deductive codes were generated from the project research questions, inductive codes presented themselves as patterns within the data.

Table 1 provides outline demographic information for questionnaire respondents, and the people they care for. The majority of respondents were women (n=128, 69.2%) caring for roughly equal numbers of men (87, 47%) and women (97, 52.5%). Respondents were overwhelmingly white (97.2%) and heterosexual (97.3%), with a mean age of 62.2 years. A majority identified their religion as Christian (n = 139, 75.1%). Most carers (n = 143, 77.3%) reported no disability, though just under a

[53] Most focus group and interview participants were recruited from respondents to the questionnaire. A total of 190 individuals participated in the research.

quarter (n = 42, 22.7%) reported having a disability, including: arthritis, cancer, diabetes and mobility impairment.

Table 1: Questionnaire Demographics						
	Carers			**People with dementia**		
Age Range	Min	Max	Mean	Min	Max	Mean
Years	26	87	62.6	44	97	76.2
	N	%		N	%	
Gender						
Female	128	69.2		97	52.5	
Male	56	30.3		87	47	
Total[54]	184	99.5		184	99.5	
Race						
White British	161	87		157	84.9	
White Irish	6	3.2		7	3.8	
White Other	13	7		16	8.6	
Mixed (White and Asian)	1	0.5		2	1.1	
Black African	1	0.5		0	0	
Asian Other	1	0.5		0	0	
Mixed (Other)	0	0		1	0.5	
Total	183	98.9		183	98.9	
Disability						
Reported disability	42	22.7		140	75.7	
No disability	143	77.3		45	24.3	
Total	185	100		185	100	
Sexual Orientation						
Heterosexual	180	97.3		180	97.3	
Bisexual	2	1.1		0	0	
Total	182	98.4		180	97.3	
Religion						
No religion	37	20		30	16.2	
Christian	139	75.1		149	80.5	
Buddhist	2	1.1		0	0	
Jewish	2	1.1		0	0	
Muslim	1	0.5		3	1.6	
Other	3	1.6		2	1.1	
Total	185	100		185	100	
Self-defined Social Class						
Middle Class	109	58.9		100	54.1	
Working Class	73	39.5		77	41.6	
Other	1	0.5				
Total	183	98.9		177	95.7	

[54] Where totals do not add to n=185/100% this is due to missing responses

Table 2: Focus Group Demographics

Pseudonym	Age	Class	Person care for/ age	Type of dementia	Residence of PWD	Caring Status
Chloe (FG1)	58	Middle class	Mother, 84	Vascular dementia	Nursing home	Ex-carer
Laura (FG1)	55	Working class	Father, 88	Vascular dementia	Nursing home	Current
Peter (FG1)	58	Working class	Mother, 92	Mixed: Alzheimer's and Vascular	Own home	Current
Viv (FG2)	64	Middle class	Husband, 68	Parkinson's disease with Lewy Body Dementia	Own home	Current
Morris (FG2)	78	Middle class	Wife, 71	Front-temporal dementia	Own home	Current
James (FG2)	47	Middle class	Mother, 77	Vascular dementia	Own home	Ex-carer
Sarah (FG2)	67	Middle class	Husband, 70	Fronto-temporal dementia	Own home	Current
Gwen (FG2)	-	Middle class	Husband, -	Lewy Body Dementia	Nursing home	Ex-carer
Graham (FG3)	87	Working class	Wife, 86	Alzheimer's	Own home	Current
Angela (FG3)	67	Middle class	Husband, 74	Alzheimer's	Nursing home	Current
Sandra (FG3)	62	Working class	Husband, 80	Vascular dementia	Nursing home	Current
Jean (FG3)	72	Middle class	Husband, 75	Alzheimer's	Nursing home	Current
Margaret (FG4)	77	Middle class	Husband, 81	Vascular dementia	Nursing home	Current
Tom (FG4)	73	Middle class	Wife, 69	Alzheimer's	Own home	Current
Alan (FG4)	59	Working class	Mother, 89	Alzheimer's	Own home	Current

Fifteen participants attended four focus groups held in two large cities and two towns in central and southern England between September and December 2011. A total of 34 people were invited to participate in focus groups, and originally 18 carers had agreed to participate, but three were not able to attend on the day. The response rate for focus group participation was therefore 44%. All

participants were white and heterosexual. In total 8 hours 40 minutes of focus data were collected, with each group lasting around 2 hours.

As we can see from Table 2, nine (60%) of the participants were women, six (40%) were men and their mean age was 66 years (range 47-87). The majority (12, 80%) were currently caring and three participants were bereaved. Ten (67%) participants defined as middle class, while five (33%) defined as working class. Ten (67%) were caring for a spouse, while five (33%) were caring for a parent. The mean age of the person the participants cared for was 78.9 years (range 69-92) and they had been diagnosed with a range of dementias: five (33%) with Alzheimer's disease; five (33%) with vascular dementia; two (13%) with Lewy Body dementia; two (13%) with fronto-temporal dementia and one with mixed Alzheimer's and vascular dementia. About half of the people with dementia resided in their own home and half in a nursing home.

Table 3: Interview Demographics

Pseudonym	Age	Class	Person care for/ age	Dementia type	Residence of PWD	Caring status
Victoria	63	Middle class	Mother, 88	Alzheimer's	Own home	Current
Carlos and Anne	58	Working class	Father, 87	Alzheimer's	Own home	Ex-carer
Jan	58	Working class	Mother, 87	Vascular dementia	Residential home	Current
Emma	79	Middle class	Husband, 83	Vascular dementia	Residential home (self-funding)	Current
Sue	59	Working class	Mother, 87	Vascular dementia	Residential home (self-funding)	Current
Derek	65	Working class	Mother, 86	Vascular dementia	Own home	Ex-carer
Maureen	60	Middle class	Mother, 95	Alzheimer's	Nursing home (self-funding)	Ex-carer
Kaylet	59	Working class	Husband, 67	Fronto-temporal dementia	Own home	Current
Jonathan	67	Middle class	Wife, 66	Fronto-temporal dementia	Nursing home (NHS continuing care)	Current
Mick	70	Working class	Wife, 68	Alzheimer's	Nursing home (NHS continuing care)	Current
Pamela	56	Middle class	Husband, 60	Fronto-temporal dementia	Own home	Current

Table 3 provides demographic information about carers who were interviewed. Interviews ranged from 1 hour 16 minutes to 2 hours 7 minutes (mean length 1 hour 37 minutes) and were conducted in participants' homes between November 2011 and January 2012. Most interviews were conducted in the Midlands, three were conducted in the North of England and two in the South. All participants were white and all identified as heterosexual apart from one bisexual woman. Eighteen potential

interviewees were invited to participate, so the response rate was 61%, although only two carers who were contacted actively declined participation. Interviewees' mean age was 63 years (range 56-79) and the mean age of the person they cared for was 79.5 years (range 60-95).

B: Statistical Findings – Antipsychotic medication

In the questionnaire, 52 carers (28.1%) reported that the person with dementia that they care for had been prescribed antipsychotic medication. This proportion roughly corresponds with the proportion of people with dementia prescribed antipsychotics identified by Banerjee in his investigation into the prescription of antipsychotic medication to people with dementia.[55] These 52 carers reported 72 prescriptions of antipsychotic medication, as several (n=15, 8.1%) reported the prescription of more than one type of antipsychotic. Table 4 provides a breakdown of the antipsychotic prescriptions. Of the types of antipsychotic medication prescribed, Risperidone, which is the only antipsychotic drug licensed for use with people with dementia, accounted for just 15 (21%) of these reported prescriptions. As such, up to 79% of the prescriptions of antipsychotic medications reported by respondents in this study may be 'off-label' prescriptions.

Table 4: Reported Prescriptions of Antipsychotic Drugs

Antipsychotic Medication	No. Reported Prescriptions
Amisulpride	4
Quetiapine	29
Risperidone	15
Chlorpromazine	3
Haloperidol	12
Promazine	3
Others	6

A series of Chi-Square analyses were run to interrogate factors that may increase the likelihood of a person with dementia being prescribed antipsychotic medication. No significant differences were found in relation to the gender or self-identified social class of either the carer or the person with dementia, nor on whether the carer lived with the person with dementia. Three statistically significant differences were found in these data. Firstly, there was a significant association between the reported diagnosis, and the prescription of antipsychotic medications, with those with a diagnosis of frontotemporal dementia (FTD) (n=17, 41.5%) and Dementia with Lewy Bodies (DLB) (n=3, 50%) more likely to report such prescriptions than those with other diagnoses ($x^2 = 21.313$, $df = 8,\ p = 0.006$). This difference can be explained, at least in part, by the different sets of symptoms that people with these rarer forms of dementia experience. These forms of dementia often have significant behavioural components, including for FTD behavioural difficulties, and for DLB fluctuating cognitive disturbance.[56] Importantly, however, the use of antipsychotic medication

[55] Banerjee (n 9).
[56] NICE Dementia, (n 5), 30.

for DLB is explicitly contra-indicated in the NICE guidance, "because those with DLB are at particular risk of severe adverse reactions".[57]

The second statistically significant finding was that carers of people with dementia who reported the prescription of antipsychotic medication were significantly more likely ($x^2 = 10.921,\ df = 1,\ p = 0.001$) to report having had cause to complain (n=31, 65.3%) about the way the person they care for was treated by professionals than those who did not report the prescription of antipsychotic drugs (n=49, 37.1%). Finally, and perhaps most interestingly, there was also a significant association between observed and expected frequencies for antipsychotics prescribed to people with dementia living in formal residential or nursing care ($x^2 = 5.344,\ df = 1,\ p = 0.021$). Carers of people with dementia living in formal care were therefore statistically significantly more likely to report that the person they care for had been prescribed antipsychotic medication. If we look solely at those people with dementia living in formal care (n=39, 22% of total respondents), the proportion of people with dementia prescribed antipsychotic medications increases to nearly one half of these (n= 17, 43.6 %). There are likely to be a number of factors that contribute to this finding, including that BPSD are factors in carer strain,[58] and in the early institutionalisation of people with dementia.[59] These are, however, statistically significant differences, which echo findings from previous research exploring these issues.[60] These statistical findings can be interrogated further by exploring the qualitative data from carers in the questionnaire, focus groups and interviews.

C: Qualitative Findings – Carers experiences of antipsychotic medication

Alongside these three statistical findings, the qualitative comments highlight three themes in respect of carers' experience of the use of antipsychotic drugs in people with dementia. Firstly, carers document the negative effects on people with dementia from the use of this class of medication. Second, they spoke of their own interventions to reduce or prevent the prescription of antipsychotics to the person they care for, including removing the person with dementia from in-patient or respite care in order to protect them from the prescription of antipsychotic medication. Finally, some respondents spoke of alternatives to antipsychotic medication for the treatment of BPSD.

Whilst only one participant spoke of what would be described in the clinical literature as a severe adverse effect: "my husband was so poorly following several near death experiences with antipsychotics" [Quest_92],[61] a variety of other harms were described by these participants. Many participants highlighted the sedative effects of these medications, for example:

[57] NICE Dementia, (n 5), 35.
[58] Thomson et al, (n 7).
[59] Banerjee et al, (n 8).
[60] *E.g.*, Banerjee (n 9); Banerjee et al, (n 8).
[61] Each qualitative excerpt is labelled with the method of collection and a unique identifier for the participant. [Quest_92] thus refers to questionnaire response ID 92. [FG2_Viv] would refer to a participant with the pseudonym 'Viv', who participated in Focus Group 2. Similarly, [Int_Kaylet] refers to the interviewee with the pseudonym 'Kaylet'. All names used are pseudonyms and any potentially identifying information has been changed.

> My Mother…was given antipsychotic drugs that turned her into a zombie. [Quest_ 62]

> I was strongly against the use of this drug [Seroquel] after it left my dad in a zombie state [Quest_88]

> He was, at one point, very much like a zombie because of the antipsychotic drugs he was on because he'd been violent. [FG3_Angela]

> They put her on these antipsychotic meds, which I've looked up on the internet and they are- I think they're being withdrawn now. They made her catatonic, basically. [Int5_Sue]

Clearly, carers find the sedative effects of antipsychotic medication distressing and unhelpful. Perhaps more importantly, these carers' experiences highlight that the use of antipsychotic medication as a means of controlling behaviour can be experienced as harmful even in the absence of "severe" side effects. Several carers attributed the prescription of antipsychotics to a lack of knowledge, training or awareness of the negative effects on people with dementia. Consider this quote from a questionnaire respondent:

> I did speak with Dr [name] about the drug he'd prescribed he said it was for my dad's depression (my dad has never suffered from depression) after researching online about this drug I went to my dad's doctor and strongly requested that my dad came off this drug as it had a black box warning and should not be used as it was for Bi-polar disorders - it stated that it should not be given to people over 65 suffering from dementia and heart problems - it was given to my dad as a suppressant - I was angry that this drug was given to my dad in the first place. I think some doctors and nursing staff have very little knowledge if any about caring for dementia people. [Quest_88]

In this excerpt, a woman (55) who provides most of the day-to-day care for her father (78) and for whom she has financial Power of Attorney (PoA),[62] describes an instance of the prescription of Seroquel.[63] She describes her use of the Internet to find out about the medication her father had been prescribed. It is clear from the way that she tells this story that not only had the prescription been 'off-label', but also that the possible adverse effects had not been discussed with her, as her father's carer. Whilst it is possible that her father had capacity to consent to this treatment at the relevant time, if he did not have capacity, then the prescriber has a duty to follow the best interests test in the Mental Capacity Act 2005 (MCA). Under the MCA, before a health professional can prescribe medication to a person who lacks the capacity to consent, they must firstly determine that

[62] In the survey we asked respondents whether they had financial power of attorney, welfare power of attorney or had been appointed as a deputy by the Court of Protection, rather than using the lasting power of attorney/enduring power of attorney distinction. Many respondents who had been caring for several years did not have the (newer) welfare power of attorney.

[63] Generic name quetiapine

it is in that person's best interests to do so. As part of the best interests determination, they must, where "practicable and appropriate" consult with and take into account the views of anyone engaged in caring for the person,[64] or any "donee of a lasting power of attorney".[65] As antipsychotic medication has a sedative effect, it is also important to consider the possibility that such a prescription may amount to restraint,[66] and could be potentially be considered to amount to a deprivation of liberty under Article 5(1) of the European Convention on Human Rights (ECHR) if "the health care professionals treating and managing the [patient] exercised complete and effective control over his care and movements."[67] In cases where there is a possibility of the deprivation of liberty,[68] then the Deprivation of Liberty Safeguards (DOLS)[69] procedures must be followed.

Mick,[70] who was interviewed for the Dementia Talking project, also spoke of his experience of looking up symptoms on the internet:

> Well I mean Kate was leaning over to side and one of things they were saying was er, she were constipated. I said "She certainly isn't constipated cos I've been there when they changed her pads." So I put this leaning into Alzheimer's website and it come up with nothing. Got onto Alzheimer's Association and they call it Pisa Syndrome. They've had it documented for ages. Put it down purely to drugs. So care home, well it were nursing home, that Kate was in at that time, I told GP about drugs, she said "Well I shouldn't touch her drugs, but seeing"- they'd just put her on, I forget what it were called, just put her on this drug. […] Anyway the- this doctor rung care home up and said "How's she doing?" She said "Oh she's still-" she were getting a bit agitated again, you know, and er so they doubled this drug. Well she started leaning more and falling, actually falling. So I told GP, and she said "Well I'll cut her back to what she was on on original dose." Well she straightened up in two days, and then it wasn't long they took her off it completely. [Int_Mick]

Clearly Mick found relevant information online that allowed him to negotiate with the GP, and question the particular prescription that had been given to his wife. He then attributes his intervention to the reduction in dose, lessening of the drug-induced dystonia his wife was suffering from and subsequent withdrawal of the medication. Several carers in our study described having to intervene when medication that they thought was inappropriate for the person they care for was prescribed:

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[64] MCA 2005, s. 4(7)(b).
[65] ibid, s. 4(7)(c)
[66] MCA 2005, s.6.
[67] *HL* v. *The United Kingdom* (Application no, 45508/99), at para 91.
[68] Note that the UK courts have recently taken a fairly restrictive approach to the definition of deprivation of liberty, particularly in respect of persons living at home or in a care home: *Surrey County Council* v. *CA and LA and MIG and MEG* [2010] EWCA Civ 190.
[69] MCA 2005, s4A and Schedule A1, as inserted by the Mental Health Act 2007, s. 50.
[70] See table 3 above.

> I was appalled at the use of anti-psychotic drugs (once I realised what they were and after I took my husband off them) in the general hospital given by medical staff who did not seem to realise their effect on someone with dementia. He was up all night and extremely confused and then slept by day once I visited him and enabled him to rest. I stayed up all one night once he was home to document their effect on my husband and then gradually took him off them. They are EVIL! … They make people worse not better and they kept increasing the dose to try and make him more 'manageable'. They failed. [Quest_ 119]

Again, in this account from a woman (62) caring for her husband (72), who reported the prescription of two different types of antipsychotic medication (quetiapine and haloperidol), there is another instance of carers clearly not being provided with full information about the off-label prescription of antipsychotic drugs ("once I realised what they were"). Here, she weaned her husband off the medication once he was home from hospital. For other carers, the prescription of antipsychotic drugs resulted in them removing their family member from formal care provision.

> Another occasion he went to a unit for assessment which was totally lacking in dementia care, he was drugged and put in a nappy when he had no continence problems, he fell and sustained a head injury as a result of this so next night he was put on the floor on a mattress. When I visited the staff supposedly caring for him were sitting watching TV while he was wandering up and down in a dazed state and when I removed him the staff became very defensive and I subsequently found that this was not an isolated incident. [Quest_63]

Here, this woman (62), who cared for her husband (now deceased), who was also prescribed quetiapine, describes a significant failure of care, which resulted in her removing him from the assessment unit prematurely. The way she describes his treatment "he was drugged and put in a nappy" suggests that the treatment he received may have been inappropriate, and was unlikely to have been in his best interests. There may even be some possibility of interference with his rights under the inhumane or degrading treatment branch of Article 3 ECHR. Many carers articulated very strong feelings about the inappropriateness of the prescription of antipsychotic medication. In a focus group, Tom[71] shared an experience from when his wife had been in respite care while he underwent major surgery:

> During the sixth week [of respite] she started having nightmares, and so they wanted to give her antipsychotics, and I said 'no'. But the doctor actually prescribed them, and I think she was given one tablet and it gave her the runs, and they didn't give her anymore. But as soon as they said that, I- although I wasn't fit enough to bring her home, I brought her home. [FG4_Tom]

Similarly, in an interview, Sue described removing her mother from in-patient care because of the effects of antipsychotic medication:

[71] For more demographic information, see Table 2, above.

> They made her catatonic, basically, she was- So we took her out … we discharged her and we took her home and she said "oh thank God I'm home." And she told me all about what had happened in hospital and how she'd had a fall unsupervised, she'd been unsupervised and gone to the toilet and had a fall. And black and blue, they made her sign a disclaimer. She told me about that. We didn't know about that. She said "they made me sign a form saying, you know, I'd been offered help and I didn't want"...something like that. [Int5_Sue]

In all three of these excerpts the familial carer describes removing the person with dementia from formal care, in an assessment unit, a respite care home and hospital respectively, because they experienced failures of care associated with the prescription of antipsychotic medication. This highlights the ways that the potential harms associated with the use of antipsychotic drugs to control BPSD are not limited to biochemical side effects of the medication (e.g. stroke, death) but also include over-sedation and exacerbation of behavioural problems, which require additional input from carers. Without such additional support, the antipsychotics can lead to the person with dementia experiencing physical injuries, falls, and heightened confusion.

Viv, whose husband has a complex diagnosis of a rarer type of dementia, and who can exhibit "very aggressive, challenging behavior" spoke of her conversation with her husband's neurologist:

> The neurologist wants to prescribe, um, antipsychotic drugs, which are now being debated as being-you shouldn't do that, you know. So the last time we went to the neurologist at [the hospital] he said 'are you using Seroquel?' I said, 'well, honestly, doctor, I prefer not to use Seroquel', I mean it's a real chemical cosh, you know, ah, and it makes him very weird. I mean, he's very weird anyway, but the Seroquel, the chemical cosh makes him, sort of, doubly bad. [FG2_Viv]

This mirrors findings from previous qualitative research with old age psychiatrists about why they prescribe antipsychotic medication to control BPSD.[72] Wood-Mitchell *et al* found that "psychiatrists often felt pressured to 'do something' and believed that in many cases non-pharmacological approaches were not feasible due to a lack of resources, time constraints and difficulties in implementation."[73] This is in contrast to the NICE guidance which suggests that all other approaches to control challenging behaviour should be attempted prior to the prescription of antipsychotics.[74] Another focus group participant, Angela, spoke of her concerns that her husband would be prescribed antipsychotics again because of his behaviour:

> Over the last weekend he's actually hit one of the nurses again. So now, of course they- they don't know why it's suddenly flared up, … he might be in pain, and he can't communicate that and so that may- may be what's making him

[72] A Wood-Mitchell, I A James, A Waterworth, A Swann and C Ballard 'Factors influencing the prescribing of medications by old age psychiatrists for behavioural and psychological symptoms of dementia: a qualitative study' (2008) 37(5) Age & Ageing 547-552.
[73] Ibid, 551.
[74] NICE Dementia, (n 5),

> frustrated and therefore he lashes out. That was waiting for me on Friday when we got home so, you know, it, I- I- I will say I don't want him to go back on the antipsychotic because it made him such a zombie but [sighs] it may be a possibility that we have to face. [FG3_Angela]

Here, it seems that Angela directly links the use of antipsychotic medication to be the possible response to a single incident. She also describes other causes for this challenging behaviour, such as pain and the inability to communicate, or frustration. Just before the above excerpt, Angela said that her husband has been taking memantine,[75] which is not an antipsychotic medication but is used to treat dementia, and which has helped to control his challenging behaviour over several months. Similarly, Mick described his experience with memantine:

> She were in a care home and they kept calling it violence and I thought it was more agitation than violence...Anyway, we were mentioning it to doctor one time and I said "What about this Memantine?" "I don't think it'll work for Kate." I said "You don't think it'll work or you- you know it won't work?" He said "I don't think it'll work." Well deal was that we tried it for three months see how she went on, and it calmed her down. I mean even when doctor came in after three months, even carers were dashing up and telling him she were a lot better, you know, and in fact she's still on Memantine. That would be- she's probably been on Memantine two years. [Int10_Mick]

Memantine is one of the four medications licensed for treatment of the cognitive symptoms of dementia. Memantine is specifically licensed for use in people with moderate to severe Alzheimer's disease, and following the most recent NICE-SCIE Dementia Guideline, can be prescribed for the treatment of cognitive symptoms of moderate to severe Alzheimer's disease,[76] and "some behavioural effects have been noted."[77] Importantly, therefore, there are other medications that have been proven to help with reducing challenging behaviour in people with dementia. Consider also this excerpt from Tom, during a discussion about antipsychotic medication:

> As I say, there must be cases where it's appropriate, but most aren't. And paracetamol, I know a case where it's worked wonders. [FG4_Tom]

Here, Tom is referring to research published by the BMJ in 2011 that found a significant reduction in agitation in people with dementia on a number of measures following an eight-week treatment intervention with analgesics.[78] Findings from research such as this may signal a move away from the use of antipsychotic medication as a first line response to BPSD. Importantly, however, as well as the possibility of prescribing analgesics or memantine to treat BPSD, the increased attention given to

[75] Memantine is licensed for the treatment of moderate to severe Alzheimer's disease.
[76] NICE Dementia, (n 5), 25.
[77] NICE Dementia, (n 5), 95.
[78] BS Husebo, C Ballard, R Sandvik, O Bjarte Nilsen, D Aarsland 'Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial' (2011) 343 British Medical Journal d4065.

antipsychotics may lead to an increase in the prescription other forms of medication, including the off-label prescription of other neuroleptic drugs that also have a sedative effect, and negative side effects.[79]

In summary, the qualitative findings from these research projects highlight that carers overwhelmingly report negative experiences of the prescription of antipsychotic medication to people with dementia.[80] In contrast to the severe adverse effects (e.g., stroke, death) of these drugs highlighted in clinical research, carers described a range of other harms experienced by the person with dementia that they care for. They described sedative effects of antipsychotics, leaving people with dementia like 'zombies' or 'catatonic'. Informal carers, including those with power of attorney, reported not being consulted prior to the use of antipsychotic medication nor given any information about the risk/benefit profile of the drugs prescribed. Several carers reported removing people with dementia from formal care settings because of failures of care associated with the prescription of antipsychotics. Finally, some carers spoke of health care professionals' reluctance to prescribe other medication that may help with the behavioural issues that were experienced by the people with dementia that they cared for, in spite of evidence that these alternatives may be effective. All of this qualitative evidence works together with the statistical findings outlined above to provide an overview of carers' experiences of the use of antipsychotic medication in people with dementia. In particular, the experiences recounted by carers provide ample evidence of why carers who had reported the prescription of antipsychotic medication reported higher levels of 'cause to complain'.

In the next part, we draw together the regulatory framework for off-label prescription, the documented risks of serious adverse effects from the off-label prescription of antipsychotic medication, and carers' experiences of this in practice to explore the legal options for individual redress for harm, and the potential for regulatory reform in respect of off-label prescription. Before exploring the particular legal issues associated with off-label prescribing practices, it is essential to be clear that the flexibility to prescribe medicines off-label is an essential part of medical practice, and our aim in this article is not to argue for this flexibility to be withdrawn from medical professionals. Rather, our argument is that because there is a potentially higher risk of harm to patients from off-label prescription, it should be subject to greater regulatory control, and that there should be redress available where a patient is harmed as a result of off-label prescription.[81]

III: LEGAL REDRESS FOR HARM FROM OFF-LABEL PRESCRIPTION OF ANTIPSYCHOTICS IN DEMENTIA CARE

The system for licensing medications described in part one has the primary aim of protecting and promoting public health. Where medications are prescribed or supplied in accordance with their marketing authorisation, there are a number of avenues for redress available to a consumer who is harmed by using the medication. The most straightforward of these is the products liability regime.

[79] Including benzodiazepines, hypnotics, anticonvulsants and antidepressants – see Banerjee, (n 9).
[80] *Eisai* v *NICE* [2007] EWHC 1941 provides an interesting discussion of whether benefits or detriments to carers can be regarded as benefits to patients.
[81] We limit our discussion in this paper to the possibility of civil redress. We do not consider here any possible criminal liability for harm caused, nor the relevance of the offence of ill-treatment and neglect codified in Mental Capacity Act 2005, s. 44.

Under the Consumer Protection Act 1987 (CPA), a consumer is entitled to a remedy where the safety of a product (including medicines) is "not such as persons generally are entitled to expect."[82] This product liability regime is a strict liability compensation regime, and where, for example, there is a manufacturing defect in a medication prescribed in accordance with its marketing authorisation, there would be a clear route to redress. Conversely, where a medication is prescribed off-label, it would extremely difficult to claim that any adverse effects amounted to a defect in the medication (particularly if such adverse effects were documented, as is the case with antipsychotic medications and dementia). Potential claims under the CPA are also subject to a ten year time limit from the date a product is first marketed, [83] which would also rule out claims in respect of many typical and atypical antipsychotic drugs. The CPA is therefore unlikely to prove a fruitful avenue for redress for people with dementia who suffer adverse effects from the off-label prescription of antipsychotics.

A second route to redress for a person who purchases general sale list medicines, pharmacy medicines, or prescription-only medications on a private prescription would be through the ordinary contractual remedies that apply to consumers. So, for example, a remedy through the Sale of Goods Act 1979 may be available to a consumer where the medicine did not correspond with its description or is not of satisfactory quality.[84] Where medications are prescribed on the NHS, however, there is no sale, and therefore there would be no route to redress through the law of contract,[85] irrespective of whether a medication is prescribed as per the marketing authorisation or off-label. Given that these two routes to redress from the manufacturer and from the vendor of medications are therefore unavailable to people with dementia harmed by the prescription of antipsychotic medications off-label on the NHS, the only remaining avenue for redress is that provided by the tort of negligence.

There are two possible approaches that could form the basis of a cause of action for a person with dementia harmed by the prescription of antipsychotic medication: first, if they were not adequately consulted about the possible risks, they could argue that, following *Chester* v *Afshar*[86] the prescriber did not sufficiently discharge their duty to warn of the risks. Second, they could argue, that the off-label prescription of antipsychotic medication fell below the standard of care required of a medical professional. We discuss each of these examples in turn.

A: Failure to Warn of Risks as Breach of Duty

One approach that may be available to a person with dementia harmed by the off-label prescription of antipsychotics would be, following *Chester v Afshar*[87], that the relevant breach of duty was the failure to warn of the risks associated with the prescription of this type of medication. The relevant rule of law is that a patient has a right to be told if there is "a significant risk that would affect the judgment of the reasonable patient" [88] in order to give her informed consent to the treatment. In

[82] Consumer Protection Act 1987, s. 3(1).
[83] Limitation Act 1980, s. 11A, as inserted by Consumer Protection Act 1987, sched. 1.
[84] Sale of Goods Act 1979 s 14(2) - (3).
[85] *Pfizer Corporation* v *Minister for Health* [1965] 2 WLR 387.
[86] [2004] UKHL 41.
[87] ibid
[88] *Pearce v United Bristol Healthcare NHS Trust* [1999] E.C.C. 167 at [21] per Lord Woolf MR.

Chester v *Afshar*,[89] the risk in question was a 1-2% chance of paralysis following neurosurgery. In the situation we are concerned with here, the risks in question would include the increased risk of severe adverse effects including stroke, and death, as well as the more 'minor' risks of over-sedation, falls, accelerated cognitive decline and tardive dyskinesia.

The source of this right to be warned of the risks inherent in medical treatment has been said to lie with the individual right to autonomy, and more specifically, the right of a patient to decide whether or not to undergo treatment. As Lord Steyn put it: "in modern law medical paternalism no longer rules and a patient has a prima facie right to be informed by a surgeon of a small, but well established, risk of serious injury as a result of surgery."[90] In ordinary circumstances, therefore, a medical professional who prescribed a drug that carried a risk of serious side effects, without first warning the patient of those side effects would lay himself open to a claim in negligence for breach of his duty to warn of significant risks. Inevitably, because we are focusing on the treatment of people with dementia, the issue of failure to warn of risks will often be more complex, because the question of capacity to consent to treatment will often arise.

Under the MCA, everyone who has the capacity to make their own decisions must be supported to do so.[91] Where a person lacks the capacity[92] to make a decision,[93] then any decisions made on behalf of that person must be in their best interests.[94] The MCA effectively translated the common law best interest tests[95] into legislative form. Statute now requires that where a doctor treats a patient who lacks the capacity to consent in their best interests, they must consider "the person's past and present wishes and feelings (and, in particular, and relevant written statement made by him when he had capacity)"[96] as well as the views of any named consultees, carers, anyone with Power of Attorney, or who has been appointed as a deputy.[97] The English courts have not yet, to our knowledge, had the opportunity to determine how this duty to warn of the risks of a particular course of medical treatment would interact with the best interests test in the MCA.

It is possible that a breach of this duty would arise if a person with dementia was treated with an off-label prescription of antipsychotic drugs at a time when she lacked the capacity to consent to such treatment, and if neither she nor her carer (or any relevant deputy or attorney) were warned of the risks of stroke and death. However, given the MCA requirement prior to treatment in the best interests of an incapacitated patient is simply to *consult* with carers, deputies or attorneys, and to *consider* the previous wishes of the patient, it may be difficult to establish a breach of duty.[98] This is because "there is sufficient compliance with this section if…he reasonably believes that what he

[89] [2004] UKHL 41.
[90] Ibid, at [16].
[91] MCA 2005, s. 1.
[92] Ibid, s. 2.
[93] Ibid, s. 3.
[94] Ibid, s. 4.
[95] M Donnelly 'Best interests, patient participation and the Mental Capacity Act 2005' (2009) 17(1) *Medical Law Review* 1-29.
[96] MCA 2005, s. 4(6)(a)
[97] Ibid, s. 4(7).
[98] Ibid.

does or decides is in the best interests of the person concerned."[99] Importantly, however, even if a breach of duty were established, following this line of reasoning, the claimant would still need to prove that the harm was caused by the failure to warn of the risks, rather than the prescription of the medication itself. In other words, they would need to successfully argue that had they been warned of the risks they would not have consented to, or would have objected to the treatment being administered, and that this would have prevented the medication being prescribed or administered. On balance, we consider it unlikely that a claim along these lines would have significant success, given the prevalence of the use of antipsychotic medication in treating BPSD.

B: Prescription of Antipsychotics as Breach of Duty

An alternative argument would be that the off-label prescription of antipsychotic medication *per se* fell below the required standard of care. The development of the concept of standard of care in medical negligence since *Bolam* has been the subject of extensive attention from legal scholars, and there is not space to rehearse these arguments here.[100] In particular there has been a feeling that the courts have been, at times, been excessively deferential to the medical profession[101] in determining whether a particular treatment regime or course of action was negligent. As such, given that the prescription of antipsychotics to control BPSD has been commonplace for a considerable period of time (in spite of the established risks and potential harms outlined above) it is unlikely that on application of the *Bolam* test alone, a person with dementia would succeed with an argument that the treatment fell below the standard of care required.

There are two relatively recent developments that may increase the potential for success in a case of harm caused by antipsychotics prescribed for BPSD: first, the effect of Lord Browne-Wilkinson's reasoning in *Bolitho*,[102] and second, the contemporaneous rise of the use of guidelines in medical practice. In the decade and a half or so since the decision in *Bolitho*, it has become apparent that its impact has been relatively modest.[103] The facts of *Bolitho* have been well-rehearsed in the literature, but in brief, this case concerned a claim of negligence in respect of a two-year-old child with respiratory failure. The child suffered brain damage, and claimed that this was caused by the negligence of a doctor in firstly failing to attend, and secondly failing to intubate. The doctor claimed that even if she had attended, she would not have intubated and thus the case failed on the issue of causation.[104] More importantly, for the present discussion, however is the now famous dicta of Lord Browne Wilkinson, revising the *Bolam* test to the extent that the court is able to disregard expert medical evidence that does not withstand logical analysis:

> In the vast majority of cases the fact that distinguished experts in the field are of a particular opinion will demonstrate the reasonableness of that opinion. In

[99] Ibid, s.4(9).
[100] For a detailed consideration of this voluminous literature, see M Brazier and J Miola, 'Bye Bye *Bolam*: A medical litigation revolution?' (2000) 8 Medical Law Review 85-114.
[101] The Right Honorable the Lord Woolfe 'Are the Courts Excessively Deferential to the Medical Profession?' (2001) 9 Medical Law Review 1-16.
[102] *Bolitho (Deceased)* v *City and Hackney Health Authority* [1998] AC 232.
[103] R Mulheron (2010) 'Trumping *Bolam*: A critical legal analysis of *Bolitho's* "Gloss"' (2010) 69(3) Cambridge Law Journal 609-638.
[104] For an overview of the causation issues in *Bolitho*, see R Heywood 'The logic of *Bolitho*' (2006) 22(4) Professional Negligence 225-235.

> particular, where there are questions of assessment of the relative risks and benefits of adopting a particular medical practice, a reasonable view necessarily presupposes that the relative risks and benefits have been weighted by the experts in forming their opinions. But if, in a rare case, it can be demonstrated that the professional opinion is not capable of withstanding logical analysis, the judge is entitled to hold that the body of opinion is not reasonable or responsible.[105]

In *Bolitho,* on the facts, the court did not determine that there had been negligence, nor that the expert professional opinion was not capable of withstanding logical analysis. The court determined, rather, that the negligence in the case was the doctor's failure to attend, not the failure to intubate. Importantly though, the decision in *Bolitho* was to certain extents a restatement of a principle from a much older case, *Hucks* v *Cole*,[106] decided in 1954, and reported in 1993. In this case, a pregnant woman was suffering from an infection, which was inadequately treated, and could have been easily resolved with a course of penicillin. She subsequently became seriously ill with puerperal fever. Medical experts on behalf of the defendant agreed they would have done the same thing, but the court found the doctor negligent: "When the evidence shows that a lacuna in professional practice exists by which risks of grave danger are knowingly taken, then, however small the risks, the court must anxiously examine that lacuna - particularly if the risks can be easily and inexpensively avoided."[107] The reasoning in *Hucks* v *Cole* does seem to offer scope for the development of an argument about the relative seriousness of the risks associated with the prescription of antipsychotics to people with dementia (including death, stroke, interference with human rights, over-sedation etc) as compared to the limited evidence of benefit of prescribing these drugs (e.g., high placebo effect in clinical trials). It is possible, therefore, that the *Bolitho* formulation of the *Bolam* test may offer an avenue for a test case exploring negligence liability in respect of the off-label prescription of antipsychotic medication.

C: The Role of Clinical Guidance in Prescribing Antipsychotics for BPSD

In order to assess whether there would be a likelihood of success in either of these types of claim, it is important to evaluate whether 'the respectable body of professional opinion' that supports the use of antipsychotic medication in BPSD is capable of 'withstanding logical analysis'. Given the rise of the use of guidelines in medical practice, and the increasing likelihood of the use of these by lawyers in medical negligence claims,[108] it seems appropriate to explore the relevant clinical guidelines that cover the treatment of BPSD.

There are two sets of UK clinical guidelines that would be relevant to determining the appropriate standard of care for using pharmacological treatments in the management of challenging behaviour in dementia, the NICE/SCIE Guideline on Dementia[109] and the Royal College of Psychiatrists Faculty

[105] *Bolitho*, (n 85), per Lord Browne-Wilkinson at 243.
[106] [1993] 4 Med LR 393.
[107] ibid, per Sachs LJ.
[108] A Samanta, M Mello, C Foster, J Tingle and J Samanta 'The Role of Clinical Guidelines in Medical Negligence Litigation: A shift from the *Bolam* standard?' (2006) 14 *Medical Law Review* 321-366.
[109] NICE Dementia, (n 5).

of Old Age Psychiatrists Guidance (RCPsych Guidance).[110] The NICE/SCIE guideline was first published in 2006 (updated in 2011) and represents a comprehensive overview of the "identification, treatment and care of people with dementia and the support that should be provided for carers within primary and secondary healthcare, and social care."[111] In contrast, the relevant RCPsych Guidance was issued in 2005, has the issue of management of BPSD as its focus, and does not appear to have been updated in the intervening period. Both documents offer guidance on the prescription of antipsychotic medication for the treatment of BPSD.

Importantly, in the context of evaluating the use of guidelines in medical negligence claims, there are some significant differences in the guidance issued to practitioners in each of these documents. In respect of treating "mild to moderate non-cognitive symptoms" the NICE/SCIE guideline has a much less permissive approach to the issue than the RCPsych document. The NICE guideline states:

> 1.7.2.2 People with Alzheimer's disease, vascular dementia or mixed dementias with mild-to-moderate non-cognitive symptoms should not be prescribed antipsychotic drugs because of the possible increased risk of cerebrovascular adverse events and death. [112]

In contrast, the RCPsych guidance suggests that it is appropriate to use antipsychotic medication as a first-line approach, even in respect of mild or moderate symptoms:

> Drugs may be an appropriate first response to BPSD symptoms in the following situations: where drugs have a specific indication (e.g. depression or psychosis), whatever the severity and frequency of the symptom…For less severe BPSD and where management is not urgent then any combination of drug, environmental manipulation or behavioural treatments may be appropriate first-line approaches.[113]

The disparity in the guidance relating to severe symptoms is similarly interesting. NICE/SCIE guidance states:

> 1.7.2.4 People with Alzheimer's disease, vascular dementia, mixed dementias or DLB with severe non-cognitive symptoms (psychosis and/or agitated behaviour causing significant distress) may be offered treatment with an antipsychotic drug after the following [eight] conditions have been met.[114]

[110] RCPsych 2004 (n 44)
[111] Social Care Institute for Excellence, available at http://www.scie.org.uk/publications/misc/dementia/index.asp accessed 01 March 12.
[112] NICE Dementia (n 5), 29.
[113] RCPsych 2004 (n 44), 2.
[114] NICE Dementia (n 5), 29.

The eight conditions for prescribing antipsychotic medication include "full discussion with the person with dementia and/or carers about the possible benefits and risks of treatment. In particular, cerebrovascular risk factors should be assessed and the possible increased risk of stroke/transient ischaemic attack and possible adverse effects on cognition discussed", as well as guidance about recording, individual risk-benefit analysis and regular reviewing of the medication.

The RCPsych guidance, in contrast, states:

> Drugs may be an appropriate first response to BPSD symptoms…where the problem symptom is severe and treatment is needed quickly, for example if the target symptoms are severe (i.e. dangerous or distressing to the patient or others) and the behaviours have no clear situational trigger or occur in a setting where carers cannot cope with serious behaviour problems. [115]

The RCPsych guidance does not require the same level of consultation with the person with dementia or their carer about the risks of adverse effects as are set out in the NICE/SCIE document. Rather, the RCPsych guideline states:

> If the patient has the capacity to understand these risks and benefits of treatment approaches, then consent to treatment should be sought. If the patient does not have this capacity, then these risks and benefits should, where practical, be discussed and communicated to the general practitioner, relatives and carers. Ultimately the clinician has the responsibility for the decision to implement treatment. Relatives cannot consent on behalf of their incapacitated relatives. The relevant mental capacity legislation needs to be considered.[116]

Leaving aside the somewhat concerning lack of engagement with either the specifics of the best interests test that should be followed when instigating treatment in respect of persons who lack capacity, nor the duty to warn of the risks associated with any medical treatment,[117] there is clearly a difference in tone between these two sets of guidance. For the purposes of a medical negligence claim, both could be argued to set out a 'responsible body of medical opinion.' In a recent questionnaire study[118] with members of the RCPsych Faculty of Old Age Psychiatrists suggests that medical professionals are more sympathetic to the guidance issued by their own professional association than guidance issued by NICE. In their study, Haw *et al* found that all 207 old age psychiatrists who responded to the survey said that they prescribed antipsychotics to patients experiencing BSPD, most commonly prescribing quetiapine, haloperidol or risperidone.[119] Haw *et al* found that "two-thirds of respondents thought the NICE guideline on dementia was too restrictive,

[115] RCPsych 2004 (n 44), 2.
[116] RCPsych 2004 (n 44), 3.
[117] *Chester* v *Afshar* [2004] UKHL 41.
[118] C Haw, G Yorston and J Stubbs 'Guidelines on antipsychotics for dementia: are we losing our minds?' (2009) 33 The Psychiatrist 57-60.
[119] ibid, 58-59.

whereas over three-quarters felt the RCPsych 2005 guidance supported psychiatrists in prescribing these drugs to individuals with dementia."[120]

Given the disparity between the two sets of guidance, it is probable that any negligence claim concerning the prescription of antipsychotic medication would therefore rest on whether the relevant body of professional opinion could, following *Bolitho*, "withstand logical analysis".[121] There has been (perhaps surprisingly) very little medical negligence case law since *Bolitho* that has been instructive on how this phrase could be interpreted. [122] Those that have been decided on what appears to be *Bolitho* principles have, of course, been based on the specific circumstances of the case in question, rather than laying down precedent as they are determinations of deviation from the relevant standard of care.[123] Two cases where the courts have been willing to go against the testimony of expert witnesses as to the responsible body of medical opinion are *Reynolds* v *North Tyneside Health Authority*[124] and *Marriott v West Midlands Regional Health Authority.*[125] In both of these cases, the rarity of such a finding was stressed by the judge. In *Reynolds,* Gross J stated that *"*given the need for clinical judgment in areas such as medicine or midwifery, it is likely to be only in a rare case that the Court will regard it as appropriate to conclude that views genuinely held by a competent expert in the discipline in question are not capable of withstanding logical analysis and are hence unreasonable."[126] Given the findings from Haw *et al*, there would be no shortage of psychiatrists willing to provide expert testimony that the RCPsych guidance represents a responsible body of professional opinion. As there is one antipsychotic medication licensed for the treatment of BPSD, it would be extremely difficult to argue that the (admittedly serious) risks of prescribing this type of medication always outweighed any benefits, or even that the risks outweighed the potential benefits in any particular case. Taken together, it is therefore unlikely that a person with dementia would have much chance of bringing a successful claim under the tort of negligence, even with the extended *Bolitho* interpretation of the *Bolam* test, and with the increased reliance on clinical guidance in medical negligence cases.

IV: CONCLUSIONS - INCREASED REGULATION OF OFF-LABEL PRESCRIPTION

It is clear from the analysis in part 3 that current legal frameworks offer little chance of redress to a person with dementia harmed by the prescription of antipsychotic medication. Claims under statutory frameworks such as the Consumer Protection Act 1987 or the Sale of Goods Act 1979 would fail, and medical negligence claims would be unlikely to succeed. Given the magnitude of harm experienced by people with dementia when these medications are prescribed, as demonstrated above, we argue that there is a strong argument for increased regulation of the prescription of these medications to people with dementia. In this final part, we set out why we think that the best way to regulate the over-prescription of antipsychotic medication would be to introduce controls on the off-label prescription of all pharmaceutical products. We argue that controls on off-label prescription should include: 1) the recording of evidence that a discussion has

[120] ibid, 59
[121] *Bolitho*, (n 85).
[122] Mulheron, (n 86).
[123] ibid, 617-618.
[124] [2002] Lloyd's Rep Med 459.
[125] [1999] Lloyd's Rep Med 23.
[126] *Reynolds* v *North Tyneside Health Authority* [2002] Lloyd's Rep Med 459 at [19(5)]

taken place between the prescriber and the patient or their representative that a) the drug in question is not licensed for the use it is being put, and b) the risk/benefit profile of the off-label use of that medication; 2) a written record of a review framework for the prescription, including written records of reviews when they are undertaken; 3) explicit reference to any clinical guidance that permits or recommends the off-label use; 4) formalised frameworks for recording adverse effects (similar to the Black Triangle scheme currently used for new medications); and 5) clear routes to redress for patients or their representatives harmed by drugs that are prescribed off-label, or where the procedure has not been followed.

In his report into the prescription of antipsychotic medication, Banerjee advised against the wholesale outlawing of antipsychotics for the treatment of people with dementia, preferring instead to recommend a voluntary reduction in prescriptions (by two-thirds) as a clinical governance priority.[127] He recommended "an audit to generate data on the use of antipsychotic medication for people with dementia in each primary care trust in England."[128] The initial results of this audit were published in July 2012,[129] and will provide baseline data against which to measure the recommended reduction in the prescription of antipsychotic medication. His reasons against introducing a wholesale ban on these prescriptions included: the need to allow treatment for those people with BPSD for whom antipsychotic medication is the appropriate response (estimated at 36,000 of the 180,000 people prescribed these medications annually);[130] the possible negative effects of abrupt withdrawal from this treatment of those people currently prescribed antipsychotics;[131] the effects of primary care services changing their referral behaviour, thus unsustainably increasing the burden on community mental health teams for older people;[132] and the possibility of a "jump to different classes of ineffective medication being used."[133] In addition, Banerjee noted that increasing the complexity of prescription of antipsychotics "by making it bureaucratically complicated to initiate or maintain them" might be detrimental to "those who need to have these medications prescribed for other illnesses such as schizophrenia and bipolar disorder", [134] demonising the medication and increasing the stigma of mental health problems. All of these are, of course, important considerations, but they could be addressed if these medications were controlled through increased regulation of off-label prescriptions.

If controls on the prescription of antipsychotic medication were only introduced in respect of the off-label use of these drugs, then there would be no effect on their prescription for licensed indications, such as schizophrenia and bipolar disorder, nor on the use of Risperidone, the one antipsychotic that does have an MHRA marketing authorisation that covers BPSD. There would similarly be no need for the immediate withdrawal of drugs for those already prescribed them 'off-label', though there would be an argument for introducing a requirement for prescribers to initiate a

[127] Banerjee (n 5).
[128] ibid, 8.
[129] 'National Dementia and Antipsychotic Prescribing Audit', available at http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/national-dementia-and-antipsychotic-prescribing-audit accessed on 24 July 2012.
[130] ibid, 3.
[131] ibid, 37.
[132] ibid
[133] ibid, 45. Such different classes of medication might include sedatives, or other neuroleptic medications.
[134] ibid.

review of all those who are currently prescribed medication off-label. Controls on off-label prescriptions would also prevent prescribers from simply switching from using antipsychotics to using off-label prescriptions of other neuroleptic drugs that are of similarly unproven effectiveness, or have different adverse side effect profiles. Introducing controls on off-label prescription would also have the benefit of ensuring that healthcare professionals engage in evidence-based practice wherever possible. It would provide a framework for gathering evidence of adverse effects, and for patient benefit. It would also ensure that medical professionals fulfil their responsibilities under the Mental Capacity Act 2005 when treating people who lack capacity in their best interests. Such a regulatory process would also protect other vulnerable patient groups from potential harms associated with off-label prescription, whilst concurrently continuing to allow medical professionals the flexibility to prescribe off-label where they think this is the best treatment for their patients.

Finally, introducing tighter legal controls on off-label prescribing practices would have the secondary benefit of encouraging pharmaceutical companies to carry out the clinical tests necessary to determine the safety of alternate uses of their medications and thus increase the licensed treatments available. If existing medications were found not to have the safety profile necessary to be licensed for treating those conditions that they have been routinely prescribed off-label for, this would encourage the development of more effective medications, and save the costs of ineffective and unnecessary off-label prescription.