Management

10

Contents

Abstract

This chapter examines various aspects of the management of cognitive disorders, including provision of information and pharmacotherapy, both licensed and novel treatments. The effects of a number of policy directives issued under the auspices of the United Kingdom government in recent years are examined: none appears to contribute to closure of the dementia diagnosis gap. The place of neurology-led services for dementia within an integrated dementia care pathway is considered.

A. J. Larner, *Dementia in Clinical Practice: A Neurological Perspective*,
https://doi.org/10.1007/978-3-319-75259-4_10

Keywords
Dementia · Treatment · Cholinesterase inhibitors · National Dementia Strategy · Integrated care pathway

The management of dementia syndromes is a broad topic, encompassing not only pharmacotherapies and behavioural therapies for cognitive deficits and physical comorbidities but also the social care context (e.g. Scharre 2010; Curran and Wattis 2011; Kurrle et al. 2012; Lipton and Marshall 2013; Rabins et al. 2016). Dementia transcends medical, social, economic and political boundaries, hence the need for enunciation of management strategies at national and international political levels (Larner 2018a). The National Dementia Strategy for England as originally conceived (Department of Health 2008, 2009; Sect. 10.5.3) included amongst its objectives an information campaign to raise awareness of dementia and reduce stigma, and improvement of community personal support services, housing support and care homes. Clearly many of these objectives fall largely or entirely outwith the sphere of neurological expertise or influence (Larner 2009a). Those with a neurological training will obviously focus on pharmacotherapy, and since Alzheimer's disease (AD) is the most common dementia syndrome much of the emphasis here will be on the treatment of this condition. Symptomatic treatment of complicating factors (e.g. behavioural and psychological symptoms, epileptic seizures) is not discussed here (for epilepsy, see Sect. 8.2.3). It has been suggested that the term "dysmentia" be used in place of dementia both to counter therapeutic nihilism and to emphasize the potential for treatment in these syndromes (Chiu 1994).

10.1 Information Seeking

With the onset of cognitive problems, and with the establishment of a diagnosis of dementia, patients and their carers may wish to seek additional information, over and above that communicated to them in clinical settings. Such sources of information include self- or relative-directed searches of the internet, and contact with patient support organisations such as the Alzheimer's Society.

10.1.1 The Internet

The Internet is a vast resource for medical information, albeit unregulated. Studies of new referrals to general neurology outpatient clinics ($n > 2000$) over the decade 2001–2010 (Larner 2006a, 2011a) have shown increasing internet access and use by patients to search for medical information prior to clinic attendance. Both access to and use of the internet was highest in younger patients, maximal in the 31–40 years age group, with least access and use in older people (i.e. those at greatest risk of dementia; Larner 2011a:29–30; b, c).

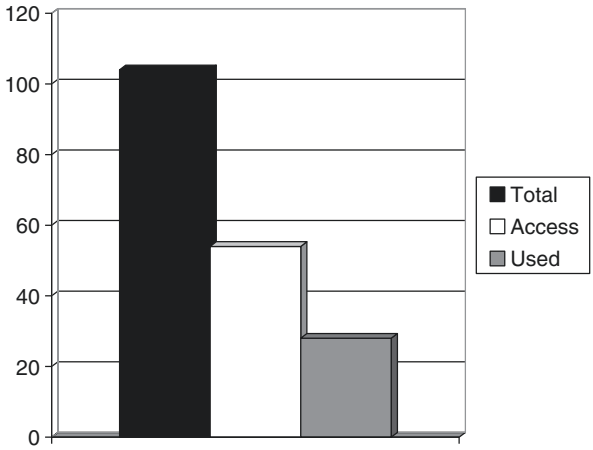

Fig. 10.1 Internet access and use by patients and carers, Cognitive Function Clinic, October 2001–March 2002 (Larner 2011a:34) reprinted with permission

Similar studies have been undertaken to examine how often patients with cognitive problems, or more usually their relatives, use the internet to access information (Larner 2003a, 2007a, 2011a:33–4). In a study of 104 patients seen in the Cognitive Function Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool over a 6-month period (73 new patients, 31 follow-ups), 54 (52%) acknowledged internet access, of whom 28 had searched for medical websites with relevant information (52% of those with access, or 27% of all cases). Eighty-five patients (82%) said that they would definitely or probably access websites suggested by the clinic doctor if they had internet access (Fig. 10.1; Larner 2003a).

In a study of awareness and use of complementary and alternative therapies for dementia (Larner 2007a; see Sect. 10.3.1), internet searches for information about AD had been undertaken in 49/84 cases (= 58%), most commonly by patients' children. The data suggested an increase in spontaneous searching for information by people diagnosed with dementia and their carers over the years (27% in 2003; 58% in 2007).

Reflecting the desire for information, and perhaps also the limited clinical resources available to meet the need, many web-based programmes for dementia caregiver support and education have been developed. These are designed to provide dementia caregivers with the knowledge, skills, and outlook needed to undertake and succeed in the caregiving role. Such studies generally indicate that participants feel more confident in caregiving skills and communication with family members, and that caregivers can benefit from receiving professional support via e-mails and dedicated information websites. An internet-based video conferencing support group may be associated with lower stress in coping with a care recipient's cognitive impairment and decline in function than an Internet-based chat support group. Combined internet and telephone delivery of multicomponent interventions may give more positive outcomes in reducing depression, burden and increasing self-efficacy than using either modality alone (Jackson et al. 2016). Suggestions for

online resources have been provided to patients with dementia and their carers in CFC (Larner and Storton 2011).

The Internet has been described as a psychoactive medium, and clearly there are potential harms, as well as benefits, from internet use for those with neurodegenerative disease (e.g. Larner 2006b).

10.1.2 The Alzheimer's Society

The Alzheimer's Society is a charitable patient organisation which operates throughout the United Kingdom to support patients with dementia and their carers (www.alzheimers.org.uk). Amongst its various activities, it sponsors research and publication of reports into various aspects of dementia in the UK (e.g. Alzheimer's Society 2007, 2011, 2013, 2014; Royal College of Psychiatrists/Alzheimer's Society 2006). Despite the name, support is available to patients with dementia diagnoses other than AD, for example a number of patients with frontotemporal lobar degenerations referred from CFC have been supported through the local Alzheimer's Society branch (Storton et al. 2012).

Only one-third of patients/carers questioned in the CFC AD outpatient follow-up clinic (July–December 2006) were aware of the Alzheimer's Society and its work. This increased to 100% following regular attendance of a Family Support Worker from the Alzheimer's Society at the clinic (Culshaw and Larner, unpublished observations). Patient cohorts for studies of screening instruments may be successfully recruited through the auspices of the Alzheimer's Society (see Sect. 5.3.2).

10.2 Pharmacotherapy

Currently the only medications licensed for the treatment of dementia are cholinesterase inhibitors and memantine (Rodda and Carter 2012). Such licensing is based on the outcomes of randomized controlled trials, systematic reviews and meta-analyses (e.g. van de Glind et al. 2013) although the methodology of clinical trials assessing medications for the treatment of dementia has been criticised (Thompson et al. 2012).

10.2.1 Cholinesterase Inhibitors (ChEIs) and Memantine

The existing evidence base suggests that cholinesterase inhibitors (ChEIs) do have effects, albeit modest, on both cognitive and behavioural symptoms of AD (e.g. Lanctôt et al. 2003; Ritchie et al. 2004; Whitehead et al. 2004; Birks 2006; Raina et al. 2008) although the cost-effectiveness of these benefits has been questioned (AD 2000 Collaborative Group 2004; Kaduszkiewicz et al. 2005). CFC has been involved in ChEI trials (Wilcock et al. 2003).

ChEI trial dropouts who received active medication showed less cognitive decline at follow-up than patients who received placebo (Farlow et al. 2003).

Naturalistic studies suggest that AD patients taking drugs licensed for dementia have a significantly lower risk of deterioration than those not taking these drugs (Lopez et al. 2005; Ellul et al. 2007), and their progression to nursing home placement is delayed (Lopez et al. 2002, 2005). These findings have prompted the suggestion that ChEIs may alter the natural history of AD, and may therefore have "disease-modifying" effects over and above their symptomatic action. However, there is no evidence that any one of the ChEIs prevent the progression from mild cognitive impairment (MCI) to AD in the long term (Salloway et al. 2004; Petersen et al. 2005; Feldman et al. 2007; Winblad et al. 2008), a finding confirmed by systematic reviews (Russ and Morling 2012; Masoodi 2013).

With the publication of guidance by the National Institute for Clinical Excellence (NICE) in 2001, ChEIs became widely available for the symptomatic treatment of mild-to-moderate AD in the UK (National Institute for Clinical Excellence 2001 [NICE was later rebranded as the National Institute for Health and Care Excellence]). Subsequent NICE guidance was more stringent in its recommendations, based on cost effectiveness analyses, thereby restricting ChEI use to moderate AD as defined by a Mini-Mental State Examination (MMSE) score of 10–20 (National Institute for Health and Clinical Excellence 2006). The most recent (and "final") pronouncement from NICE (2011) returns to the recommendation of ChEI use in mild disease.

An audit of practice in CFC (2001–2003 inclusive), at a time when ChEI prescription was permitted in the clinic (see Sect. 1.1, Fig. 1.1), suggested compliance with the then current NICE (2001) guidance for ChEIs, as well as drug efficacy in terms of MMSE scores in the short term (up to 16 months of treatment) (Larner 2004a). The majority of AD patients remained on medication beyond 6 months, contrary to the assumption of the NICE guidance that perhaps only half to two-thirds of patients would show sufficient response, with the unresponsive remainder stopping treatment (National Institute for Clinical Excellence 2001). Long term retention time has been used previously as a surrogate global measure of drug efficacy, as well as of tolerability (e.g. Marson et al. 2007). The possibility that this observation of high retention rate might have been related to the fact that patients in this cohort were younger than those examined in the pivotal clinical trials was considered, but in fact younger patients (<65 years of age) appeared to respond no differently to ChEIs than older patients (Larner 2004a), contrary to the findings in a prior report (Evans et al. 2000).

In the aforementioned audit, and in subsequent clinical experience, ChEIs have generally been extremely well tolerated (Larner 2004a), with less than 5% of patients developing gastrointestinal adverse effects. These findings are commensurate with those of systematic reviews. Headache has sometimes been mentioned as an adverse effect of ChEIs (e.g. Whitehead et al. 2004), but in a cohort of 143 patients treated with ChEIs in CFC only two developed headache, and in one of these patients the symptoms were transient and did not recur on rechallenge (Larner 2006c). Use of transdermal formulations may potentially reduce adverse effects of ChEIs by lowering the maximum plasma concentration (C_{max}) and time to reach C_{max} but with comparable drug exposure (area under the curve) (Winblad et al. 2007; Larner 2010a).

Monitoring the treatment effect of ChEIs by means of MMSE scores (see Sect. 4.1.1), as recommended by NICE (National Institute for Clinical Excellence 2001; National Institute for Health and Clinical Excellence 2006), is difficult to justify for a variety of reasons, including the variable natural history of AD as judged by MMSE scores (Holmes and Lovestone 2003), inter-rater errors in scoring the attention/calculation section of the MMSE (Davey and Jamieson 2004), and the inadequacy of the MMSE for detecting the small changes in cognition which ChEIs might produce (Bowie et al. 1999). This latter problem, measuring change in a manner relevant to the clinical problem of progressive dementia, was foreseen some years earlier when trials of anti-dementia drugs were in their infancy (Swash et al. 1991). Another issue which may require consideration is patient anxiety in the face of cognitive testing which, despite their forgetfulness, they know might lead to cessation of drug therapy, which might be termed an example of the "Godot syndrome" (Larner and Doran 2002).

ChEIs have also been examined in a number of other conditions which cause cognitive impairment (Box 10.1) (Larner 2010b; Li et al. 2015), some in clinical trials, but in many off-licence. For example, they have been reported to have clinical effects in dementia with Lewy bodies (McKeith et al. 2000), Parkinson's disease dementia (PDD; Emre et al. 2004; Dubois et al. 2012), vascular cognitive impairment (Erkinjuntti et al. 2004), and multiple sclerosis (Krupp et al. 2004). However, only in PDD has the evidence been sufficient (e.g. Rolinski et al. 2012) for ChEIs to be licensed for this indication.

Box 10.1: Conditions in which use of ChEIs has been reported (* = licensed; adapted from Larner 2010b)

Alzheimer's disease (mild*/moderate*/severe)
Mild cognitive impairment (prodromal AD)
Down syndrome
Dementia with Lewy bodies
Parkinson's disease dementia*
Progressive supranuclear palsy
Vascular dementia
CADASIL
Frontotemporal lobar degeneration
Huntington's disease
Multiple sclerosis
Cognitive impairments in epilepsy
Delirium (treatment and prevention)
Traumatic brain injury
Sleep-related disorders: obstructive sleep apnoea syndrome, narcolepsy
Psychiatric disorders: schizophrenia, bipolar disorder
Cognitive disorder in brain tumour patients
Wernicke-Korsakoff syndrome, alcohol-related dementia
Subarachnoid haemorrhage
Cerebral amyloid angiopathy

A trend of efficacy of galantamine in aphasic variant FTLD was reported by Kertesz et al. (2008) but the trial was brief and the numbers treated small. Others have also noted successful use of ChEIs in "language variants" of FTD (Lipton and Marshall 2013:87). It is perhaps possible that some of these patients may in fact harbour AD pathology as the substrate of the logopenic progressive aphasia phenotype (see Sect. 8.1.2.1). In CFC, inadvertent experience of ChEI use in FTLD misdiagnosed as AD has been uniformly negative (Davies and Larner 2009). Off licence experience with ChEIs in two multiple sclerosis patients with severe cognitive impairment has suggested limited efficacy (Larner 2010b).

The existing evidence base supports the use of the glutamate receptor antagonist memantine in AD (McShane et al. 2006; Raina et al. 2008) although NICE (2011) have ruled against its use outwith clinical trials. Combination therapy with both ChEI and memantine has been advocated, with trials suggesting both synergy (Tariot et al. 2004) and no benefit over and above ChEI use alone (Howard et al. 2012). Local funding issues have ensured that almost no experience has been gained in CFC with the use of memantine.

10.2.2 Novel Therapies

Novel dementia therapies, particularly for AD, have been developed in the hope of addressing the deficiencies of existing treatments. Some of these have reached clinical trials (Larner 2002, 2004b, 2010c; Mangialasche et al. 2010; Rafii and Aisen 2015). CFC has been involved in trials of some of these compounds through the agency of the WCNN Clinical Trials Unit (e.g. tarenflurbil: Wilcock et al. 2008; rosiglitazone; tideglusib). However, none have gained licensing approval and reached the clinical arena. Secretase inhibitors seemed to have a sound theoretical basis, designed to interrupt the biosynthetic pathway for amyloid peptides which are thought to be central to disease pathogenesis (Larner 2004b). However, the first such trialled drug (LY450139, also known as semagacestat) was withdrawn because of lack of efficacy and safety concerns (Larner 2010c; Doody et al. 2013 and http://www.nejm.org/doi/suppl/10.1056/NEJMoa1210951/suppl_file/nejmoa1210951_appendix.pdf). The increasing focus on intravenously delivered monoclonal antibody therapies for AD has not impacted on CFC practice for both economic and logistical reasons.

Treatment for other dementing conditions has lagged behind that of AD, although prion disease has evoked much research (Larner and Doran 2003; Trevitt and Collinge 2006), befitting its high public profile.

Academic interest in dementia, perhaps at least in part stimulated by increased research funding, has continued to escalate with the ultimate hope of discovering treatments to address the clinical and societal burdens of dementia. There also appears to be a political will to support this undertaking, as exemplified by a G8 summit meeting in London in December 2013 which made a bold commitment to develop a cure or treatment for dementia by 2025 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265868/2901669_G8_DementiaSummitCommunique_acc.pdf).

10.3 Other, Non-Pharmacological, Therapies

The struggle to find meaningful therapeutics for dementia has shifted the focus more towards strategies of disease prevention. Some analyses suggest a third of dementia cases may be preventable, by means of tackling issues such as smoking, depression, hearing loss, education, hypertension, diabetes, obesity, social isolation and lack of exercise (Livingston et al. 2017). However, a recent long term (ca. 30 years) follow up study found no evidence for a neuroprotective effect from physical activity (Sabia et al. 2017). The (comforting) belief that moderate alcohol consumption might be protective for brain health has also been challenged by a recent longitudinal cohort study (Topiwala et al. 2017). A definitive dementia preventative strategy has yet to evolve.

10.3.1 Complementary and Alternative Therapies (CAT)

ChEIs and memantine are far from a complete therapeutic solution to the clinical phenomenology of AD. In the absence of other licensed treatments, it is unsurprising that patients and their carers may seek complementary and alternative therapies (CAT), including "natural health products", available on a non-prescription basis. Various CAT are claimed to help memory disorders and dementia, although the evidence base supporting this conclusion is weak (Diamond et al. 2003). Nonetheless many patients use these agents.

A study of patients with probable AD ($n = 84$; time from diagnosis 3–60 months) seen for follow-up visits in CFC over a 6-month period (January–June 2006) (Larner 2007a) found that 21 (= 25%) had at one time or another used CAT for memory problems (range 1–3 medications, median 1). The most commonly used agents were ginkgo biloba (14) and vitamin E (10). Five patients mentioned that they had used omega oils (Table 10.1). Both ginkgo biloba and vitamin E have some modest evidence favouring their use in dementia (Sano et al. 1997; Oken et al. 1998; Birks and Grimley Evans 2009), although there are more recent studies suggesting that ginkgo does not reduce progression from subjective memory complaints to AD

Table 10.1 Awareness and use of CAT (adapted from Alzheimer's Disease Society (ADS) website devoted to CAT, www.alzheimer's.org.uk/After_diagnosis/Treatments/info_complementary.htm) in CFC AD population ($n = 84$) (Larner 2007a)

	Heard of?	Used?
Ginkgo (*Ginkgo biloba*)	53	14
Silymarin	3	0
Chotosan	2	0
Kami-umtan-to	0	0
Yizhi capsule	2	0
Huperazine	6	1
Lemon balm (*Melissa officinalis*)	37	0
Acupuncture	75	2
Vitamin E	72	10
Melatonin	26	0

(Vellas et al. 2012) nor that it helps cognitive impairment in multiple sclerosis (Lovera et al. 2012). Vitamin E may slow functional decline in mild-to-moderate AD (Dysken et al. 2014).

The CFC data may be compared with those from a Canadian dementia clinic study which found that about 10% of the clinic population had used complementary treatments for their cognitive problems (Hogan and Ebly 1996) and a US study of caregivers which reported that 55% had tried at least one medication to try to improve the patient's memory, most usually vitamins (Coleman et al. 1995). Just over 50% of mildly cognitively impaired patients and their caregivers attending a memory clinic were reported to be current users of natural health products, with vitamin E, ginkgo and glucosamine being the most commonly used (Sharma et al. 2006). An Australian community-based survey found that 2.8% of 60–64 year-olds reported using medications to try to enhance memory (Jorm et al. 2004).

10.3.2 Gardening

Gardening activities are sometimes used as an occupational therapy for patients with dementia (Heath 2004). Since physical and intellectual activities in midlife may protect against the development of AD (Friedland et al. 2001), it has been suggested that gardening may be one component of a healthy ageing programme to prevent dementia, through stimulation of the mind (Dowd and Davidhizar 2003).

A study of 100 consecutive community-dwelling patients with a diagnosis of dementia (F:M = 54:46, 54% female; mean age ± SD = 65.6 ± 8.3 years; age range 44–82 years), most of whom had AD (n = 87), found that of the 38 who professed a premorbid interest in gardening, 27 (= 71%) were still undertaking some gardening activity, perhaps just "pottering", weeding, cutting the grass, or attending to indoor plants. Cessation of gardening activity was due in some cases to loss of interest (sometimes rekindled after commencement of ChEI therapy), physical infirmity, loss of concentration, visual agnosia, forgetting the names of plants, not knowing when to plant things, and difficulty handling plants or garden implements, probably as a consequence of clinically apparent apraxia. An individualised approach tailored to cognitive abilities and deficits may therefore be required if gardening is contemplated as a component of occupational therapy for dementia patients (Larner 2005a).

10.4 Nursing Home Placement

Studies of the natural history of AD have indicated the limited value of rate of change of MMSE scores in assessing therapeutic responses (Holmes and Lovestone 2003). Hence the use of traditional milestones as end-points, such as nursing home placement, may be more meaningful in assessing drug efficacy, although this does require longer term follow-up than in studies using cognitive, behavioural, or functional rating scales.

Nursing home placement may itself be taken to reflect a measure of global patient function. Such an endpoint also has significant economic implications, since costs escalate greatly with nursing home placement. Interestingly, nursing home placement was the end-point in one ChEI trial, such that all costs accruing after this time point were censored, a policy which may have influenced the trialists' conclusion that ChEI are not cost effective (AD2000 Collaborative Group 2004). In long term conditions such as dementia, long term studies are required in order to answer definitively such contentious issues.

An observational study by Lopez et al. (2002) came to the conclusion that ChEIs may influence the natural history of AD, over and above their recognised symptomatic effects. In this study, the frequency of permanent nursing home placement was much lower in patients receiving ChEI (5.9%, 95% confidence interval [CI] = 1.9%–9.9%) than in untreated patients (41.5%, 95% CI = 33.2%–49.7%), suggesting a long-term beneficial effect from ChEIs. However, the possibility that these findings might represent a cohort effect cannot be entirely excluded, since it would seem likely that the patients not receiving ChEIs dated from earlier in the studied epoch (1983–1999). Moreover, it is possible that earlier referral, diagnosis, support and counselling, may have contributed to the delayed institutionalization through reduced caregiver burden (e.g. Brodaty et al. 2003). Nevertheless, the figures for nursing home placement in the untreated patients were similar to those reported in a prospective study which found 35% and 62% of "mild" and "advanced" AD cases in nursing homes after 2 years (Knopman et al. 1988). Reduced frequency of nursing home placement was also found in a study of AD patients previously commenced on donepezil as part of randomised clinical trials (Geldmacher et al. 2003). Lower risk of nursing home placement, as well as lower likelihood of disease progression, was confirmed in a further study from the Pittsburgh group examining the effects of ChEIs over 24–36 month follow up periods (Lopez et al. 2005). Long-term treatment with galantamine or other ChEIs appeared to be associated with a significant delay in the time to nursing home placement in patients with AD and AD with cerebrovascular disease (Feldman et al. 2008). Any such delay in nursing home placement may have health care cost-saving implications (Provenzano et al. 2001).

A retrospective case note audit of patients prescribed ChEIs at CFC (2001–2005 inclusive) identified 98 patients who had received ChEI for >9 months (F:M: = 54:44, 55% female; mean age at onset of treatment = 63.9 ± 7.7 years, age range 49–84 years). Of these 98 patients, 93 had AD, 60 of whom (= 65%) had early-onset AD. Other diagnoses were DLB/PDD (3) and FTLD (2). Total follow-up in this group was over 217 patient years of ChEI treatment, with mean treatment duration of 26.6 (± 13.3) months (range 9–60 months). Eight of the 98 patients had permanently entered nursing homes during the study period (= 8.2%, 95% CI = 2.7%–13.6%). Of these eight (F:M = 6:2), six had AD and two had PDD. Behavioural and psychological problems were the proximate reason for nursing home placement in all cases. Eight of the 98 patients, all with AD, had died during the study period (= 8.2%; 95% CI = 2.7%–13.6%) Of these eight (F:M = 4:4), six died from causes judged AD-related (inanition, infection), two from non-AD-related causes (one from a bowel carcinoma, one from a myocardial infarction). Only one of these eight deaths was in a nursing home resident (Larner 2007b). Hence the figures for

permanent nursing home placement in this cohort were comparable to those of Lopez et al. (2002) study (8.2% vs. 5.9%), albeit that this cohort was younger (mean age 63.9 ± 7.7 years vs. 72.7 ± 7.2 years) and that follow-up was shorter (26.6 ± 13.3 months vs. 34.6 ± 21.3 months). The lower death rate (8.2% vs. 12.6%) may be a reflection of the age disparities (Larner 2007b).

A reduced risk of nursing home placement has been noted in patients treated with the combination of ChEIs and memantine (Atri et al. 2008; Lopez et al. 2009), which might reflect a synergistic effect between these medications (Tariot et al. 2004) although this was not observed in another study (Howard et al. 2012).

10.5 Policy Consequences

The days when hospital clinicians were relatively autonomous practitioners who could decide, based on their experience and expertise, what was best for their patient are now, for good or ill, long past (a slightly different dispensation persists in UK primary care, where general practitioners are deemed to know what is best for their patients, and are therefore able to pick and choose which services they wish to use, and indeed in some locations to act as commissioners for them). Various documents, labelled as guidelines or guidance, yet adherence to which is mandatory rather than optional (sometimes with adverse financial consequences for non-adherence), have emerged from UK government sponsored bodies, ostensibly to render practice uniform, but in implementation to constrain doctors. The effects of these policies, easy enough to formulate, are seldom if ever examined, the hallmark of ideology, not science. In any arena or forum where facts are few and comment is free, evaluations of (health policy) reforms are likely to be either absent or piecemeal. Moreover a gap between policy intent and what happens in practice is well-recognised (in the bureaucratic metastory, representation is inevitably distortion). For example, use of referral guidelines for the identification of brain or central nervous system cancers ("2-week wait referrals") usually result in the referral of patients without such cancers (Abernethy Holland and Larner 2008; Panicker and Larner 2012).

All such policies or "reforms" should rightly be regarded as experiments (Campbell 1969; McKee et al. 2012) and hence should be administered (with informed consent of the target population, rather than enforced implementation) and evaluated as such. Although clinicians may feel undermined by political interference, and that they are being obligated (if not financially coerced) to make failed policies work, nevertheless there is opportunity to collect data to try to measure the outcomes of these experiments, in preparation for the hoped-for (mythical?) advent of evidence-based policy making. Some attempts have been made to do this within CFC practice.

10.5.1 NICE/SCIE (2006) Guidelines

The National Institute for Health and Clinical Excellence/Social Care Institute for Excellence (NICE/SCIE) guidelines recommended that psychiatrists, particularly old age psychiatrists, should manage the entire dementia care pathway from

Table 10.2 CFC referral numbers and sources before and after NICE/SCIE guidelines of 2006 (Larner 2009b)

	Before NICE/SCIE (2005–2006)	After NICE/SCIE (2007–2008)
New referrals seen	213	382
New referrals from psychiatrists (% of total)	49 (23)	80 (21)

diagnosis to end-of-life care, acting as a "single point of referral" for all cases (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence 2006). Neurologists were mentioned only once in the document, prompting the suggestion that the specialist dementia interests of some neurologists had been (perhaps inadvertently, perhaps wilfully) overlooked (Doran and Larner 2008). Compliance with the NICE/SCIE guidelines might have been anticipated to erode the number of general referrals to neurology-led memory clinics, and referrals to these clinics from psychiatrists in particular.

The impact of NICE/SCIE guidelines in a neurology-led memory service was examined in CFC by comparing referral numbers and source in the 2-year periods immediately before (January 2005–December 2006) and after (January 2007–December 2008) publication of the NICE/SCIE document (Larner 2009b). These data (Table 10.2) indicated a similar percentage of referrals from psychiatrists in both time periods (23% and 21% respectively). The null hypothesis tested was that the proportion of referrals from psychiatrists (see Sect. 1.2.2) was the same in cohorts referred before and after publication of the NICE/SCIE guidelines (equivalence hypothesis). The result of the χ^2 test did not permit rejection of the null hypothesis ($\chi^2 = 0.39$, df = 1, $p > 0.5$), a finding corroborated by the Z test ($Z = 0.56$, $p > 0.05$).

Whilst the NICE/SCIE guidelines might possibly have been instrumental in increasing the total number of referrals (see Sect. 1.1), by raising public and professional awareness of dementia, the evidence from this survey did not suggest that referral practice from psychiatry to neurology had changed in light of NICE/SCIE. The data suggested that psychiatrists continued to value access to a neurology-led dementia service and that, *pace* NICE/SCIE, neurologists still have a *de facto* role in the dementia care pathway (Larner 2007c, 2009b).

10.5.2 QOF Depression Indicators (2006)

The Quality and Outcomes Framework (QOF) of the general practitioner General Medical Services contract in the United Kingdom (UK), introduced in April 2006, included amongst its provisions Depression Indicator 2, viz.:

> "In those patients with a new diagnosis of depression, recorded between the preceeding 1 April to 31 March, the percentage of patients who have had an assessment of severity at the outset of treatment using an assessment tool validated for use in primary care."

Three depression severity measures were suggested: the Patient Health Questionnaire depression module, PHQ-9 (see Sect. 5.2.2); the Hospital Anxiety and Depression Scale (HADS); and the Beck Depression Inventory, Second Edition (BDI-II) (British Medical Association 2006).

Prior studies of non-overlapping cohorts of patients seen at CFC showed that the percentage of patients referred to the clinic from primary care who received a diagnosis of dementia was between 37 and 40% (relative risk of dementia in primary care referrals = 0.55 to 0.69) (Larner 2005b; Fisher and Larner 2007). Some of these non-demented patients referred from primary care may have had depression, rather than dementia, as a cause for their symptoms, and hence improvements in the diagnosis of depression in primary care, perhaps as a consequence of QOF implementation, might have been anticipated to reduce these non-dementia referrals to CFC from primary care.

To test this hypothesis, a study was undertaken to examine whether any change occurred in the frequency of non-dementia diagnoses in patients referred from primary care before and after QOF introduction (Fearn and Larner 2009). All referrals from primary care seen in the 18 month periods immediately preceding (November 2004–April 2006) and following (May 2006–October 2007) introduction of the QOF in April 2006 were examined.

The percentage of all referrals to CFC which originated from primary care was about half (Table 10.3) in both time periods ($\chi^2 = 0.88$, df = 1, $p > 0.1$; Z = 0.77, $p > 0.05$). Of the primary care referrals, about one third had dementia. The relative risk of diagnosis of dementia in a primary care referral pre- and post-QOF was 0.55 (95% confidence interval [CI] 0.40–0.74) and 0.66 (95% CI 0.49–0.89), respectively (Fearn and Larner 2009). All these findings were similar to those in previously reported cohorts from CFC (Larner 2005b; Fisher and Larner 2007).

The null hypothesis tested was that the proportion of patients referred from primary care with dementia was the same in cohorts seen both before and after introduction of the QOF Depression Indicator (equivalence hypothesis). The result of the χ^2 test did not permit rejection of the null hypothesis ($\chi^2 = 0.54$, df = 1, $p > 0.05$), a finding corroborated by the Z test (Z = 0.60, $p > 0.05$) (Fearn and Larner 2009).

This observational survey found no change in the frequency of non-demented patients referred to a dedicated dementia clinic from primary care following introduction of the QOF Depression Indicator which recommended use of validated scales to measure the severity of depression. Clearly this finding is subject to the caveats applicable to any single-centre study with relatively small patient cohorts, but if true may have various explanations, including lack of uptake of Indicator use

Table 10.3 CFC practice before and after introduction of QOF Depression Indicator of 2006 (Fearn and Larner 2009)

	Pre-QOF (Nov 2004-April 2006)	Post-QOF (May 2006–October 2007)
N	186	186
GP referrals (%)	96 (51.6)	105 (56.5)
GP referrals with dementia (%)	34 (35.4)	32 (30.5)

in primary care in this region (very few referrals letters mentioned use of either depression or cognitive scales: Fisher and Larner 2007; Menon and Larner 2011), or inefficacy of the recommended depression severity scales to differentiate depression from dementia. For example, PHQ-9 was found to be of only moderate diagnostic utility for the differentiation of depression and dementia in a clinic-based cohort (see Sect. 5.2.2; Hancock and Larner 2009). Alternatively, methodological variables, such as sample size or the use of a surrogate measure of test efficacy (referrals to a dementia clinic as a measure for change in practice) may have caused a failure to find an effect that did in fact exist (i.e. type II error).

10.5.3 National Dementia Strategy (2009)

The National Dementia Strategy (NDS) for England was officially launched on 3rd February 2009 (Department of Health 2009). It proposed three key themes to address the problem of dementia: improved awareness of the condition; early diagnosis and intervention; and higher quality of care. A pathway for NDS implementation, anticipated to roll-out over a 5-year period, was also proposed. One year on, a report into progress on NDS delivery was published (National Audit Office 2010) but this omitted frontline services since they were not anticipated to have changed, as local implementation plans were still being developed. Following a change of political regime, the *Prime Minister's Challenge on Dementia* of 2012 and 2015 sought to build on the NDS, sharing the key NDS commitment to increase dementia diagnosis rates, a necessity in view of the recognised dementia diagnosis gap (Department of Health 2012a, 2015).

The possible impact of NDS in CFC was examined by comparing referral numbers, sources, and diagnoses in the 12-month periods immediately before (February 2008–February 2009) and after (February 2009–February 2010) the NDS launch (Table 10.4; see also Table 1.2, right hand columns) (Larner 2010d). These data showed a 12% increase in new referrals seen in the second time period, with a marked increase in the percentage of referrals coming from primary care (70.2% vs. 58.2%). The null hypothesis that the proportion of new referrals from primary care was the same in the cohorts referred before and after NDS launch (equivalence hypothesis) was rejected ($\chi^2 = 6.18$, df = 1, $p < 0.01$).

A small decrease in the percentage of patients receiving a diagnosis of dementia (DSM-IV-TR criteria) was noted in the patient cohort from the second time period

Table 10.4 Referral numbers, sources and diagnoses before and after NDS launch (Larner 2010d)

	Before NDS launch (Feb 2008–Feb 2009)	After NDS launch (Feb 2009–Feb 2010)
New referrals seen	225	252
New referrals from primary care (% of total new referrals)	131 (58.2)	175 (70.2)
New diagnoses of dementia (% of total new referrals)	74 (32.9)	75 (29.8)

(29.8% vs. 32.9%). The null hypothesis that the proportion of new referrals receiving a diagnosis of dementia was the same in the two cohorts was not rejected ($\chi^2 = 0.63$, df = 1, $p > 0.1$) (Larner 2010d).

Extending this analysis to encompass the 5-year period 2009–2013 showed that referral numbers were found to have increased, most particularly those from primary care (Table 1.3). The null hypothesis that the proportion of patients referred from primary care over this period did not differ significantly was rejected ($\chi^2 = 22.1$, df = 4, $p < 0.001$). Considering patient diagnoses, the null hypothesis that the proportion of all referred patients who were diagnosed with dementia over this period did not differ significantly was not rejected ($\chi^2 = 4.03$, df = 4, $p > 0.1$), and likewise for a diagnosis of any cognitive impairment (= dementia + MCI; $\chi^2 = 3.85$, df = 4, $p > 0.1$) (Larner 2014).

These findings suggested that the NDS may have increased the total number of referrals to CFC, perhaps by raising awareness of dementia, although the initial increase was not as marked as that seen following the publication of the NICE/SCIE guidelines (see Sect. 10.5.1; Table 10.2). The post-NDS increase in referrals came mostly from primary care, supporting the contention that GPs were becoming more positive about diagnosing dementia early (National Audit Office 2010). However, there was no accompanying increase in the number of new diagnoses of dementia, and hence no evidence for closure of the dementia "diagnosis gap" (i.e. too few people being diagnosed with dementia or diagnosed early enough; it is reported that only a third to a half of people in England with AD receive a formal diagnosis: National Audit Office 2007; Alzheimer's Society 2011; 2013). The impression was that more "worried well" individuals were being referred, rather than those with previously undiagnosed dementia (see Sect. 8.3).

10.5.4 NICE Guidance (2011): Anti-Dementia Drugs

The most recent (and "final") guidance on the use of the anti-dementia drugs published by the National Institute for Health and Clinical Excellence (2011) made these drugs available as per licence, effective from 1st June 2011, and hence more easily accessible than had previously been the case following previous NICE guidance (2006). One anticipation of this liberalization of drug availability was that more people who might be candidates for licensed use of these medications (i.e. mild to moderate AD and Parkinson's disease dementia) would be referred to dementia/memory clinics, with a possible diminution in the recognised dementia "diagnosis gap" resulting from too few people being diagnosed with dementia or diagnosed early enough (Alzheimer's Society 2011, 2013).

The possible impact of the NICE 2011 guidance in a neurology-led memory service was examined by comparing referral numbers, sources, patient diagnoses and candidacy for treatment with cholinesterase inhibitors in the 12-month periods immediately before (1st June 2010–31st May 2011) and after (1st June 2011–31st May 2012) publication of the guidance (Larner 2012a). These data showed no change in numbers of new referrals between the two time periods (Table 10.5), but

Table 10.5 Referral numbers, sources, patient diagnoses and candidacy for ChEI/memantine treatment before and after NICE 2011 guidance (NICE217) effective (adapted from Larner 2012a)

	Before NICE217 effective (1 June 2010–31 May 2011)	After NICE217 effective (1 June 2011–31 May 2012)
New referrals seen	230	225
F:M (% female)	108:122 (47.0)	126:99 (56.0)
Age range (median), years	19–88 (61.5)	18–93 (61)
New referrals from primary care (% of total new referrals)	169 (73.5)	186 (82.7)
New diagnoses of dementia (% of total new referrals)	68 (29.6)	62 (27.6)
Candidacy for treatment with ChEI/memantine (% of total new referrals; % with dementia)	44 (19.1; 64.7)	44 (19.6; 71.0)

with an increase in the percentage of referrals coming from primary care in the second time period (82.7% vs. 73.5%). The null hypothesis that the proportion of new referrals from primary care was the same in the cohorts referred before and after NICE 2011 guidance (equivalence hypothesis) was rejected ($\chi^2 = 5.12$, df = 1, $p < 0.05$). However, there was no change in the percentage of patients receiving a diagnosis of dementia (DSM-IV-TR criteria; $\chi^2 = 0.17$, df = 1, $p > 0.5$).

The proportion of patients deemed candidates for treatment with ChEI/memantine was examined. Exclusions included patients with frontotemporal lobar degenerations, vascular dementia/subcortical ischaemic vascular dementia, dementia with Lewy bodies, Huntington's disease, Down syndrome, alcohol-related dementia, and prion disease, since these conditions fall outwith drug licence, although ChEI have sometimes been used in these conditions (Box 10.1; Larner 2010b). This analysis showed no change in the proportion of patients suitable for these medications, examining either the whole cohort ($\chi^2 = 0$) or those patients with dementia only ($\chi^2 = 0.56$, df = 1, $p > 0.5$).

Unlike the situation with NICE/SCIE (Sect. 10.5.1; Larner 2009b) and the National Dementia Strategy (Sect. 10.5.3; Larner 2010d, 2014), there was no increase observed in referrals to CFC following the NICE 2011 guidance on anti-dementia drugs. Of perhaps greater concern, no increase in the number of referrals deemed candidates for treatment with these drugs was observed, and hence no evidence for closure of the dementia diagnosis gap.

10.5.5 Dementia CQUIN (2012)

The Dementia Commissioning for Quality and Innovation (Dementia CQUIN) document published under the auspices of the UK Government in April 2012 (Department of Health 2012b) sought to implement a proactive approach to identify people with dementia, in part to address the dementia diagnosis gap (Alzheimer's Society 2011, 2013). Dementia CQUIN required all individuals aged 75 years or over presenting to secondary care for whatever reason to be asked a screening

question ("Have you been more forgetful in the past 12 months to the extent that it has significantly affected your life?"), which if answered in the affirmative was to trigger a "Dementia Risk Assessment". Compliance with the Dementia CQUIN was incentivised with cash payments according to level of performance. The principles of the Dementia CQUIN were also proposed for use in primary care, despite a lack of evidence for such screening (Brunet et al. 2012). Evidence for the utility of the single screening question was not presented (probably because this had not been examined); post hoc data is scant, and not compelling (see Sects. 3.1.1.1 and 3.1.1.3; Larner 2018b).

Details of the Dementia CQUIN "Dementia Risk Assessment" were unspecified, but it would seem likely that administration of some form of cognitive screening instrument (CSI) would form an integral part of any such assessment. One such CSI, the Six-Item Cognitive Impairment Test (6CIT; Sect. 4.1.6; Brooke and Bullock 1999; Gale and Larner 2017), was accepted as a Dementia CQUIN target by two NHS Trusts within the CFC catchment area (Liverpool Community Health and Bridgewater Community Healthcare).

In a prospective study, referral letters of consecutive patients seen in CFC over a 6-month period (July–December 2012) following publication of the Dementia CQUIN (April 2012) were examined for any mention of use of the 6CIT prior to referral (Cagliarini et al. 2013), a methodology used in previous studies (Fisher and Larner 2007; Menon and Larner 2011). The study found that of 132 consecutive referrals to CFC (F:M = 58:74, 44% female; age range 20–88 years, median 58 years) very few had been assessed with 6CIT prior to referral (7/132 = 5.3%), although this was an increase on previous cohorts (1/123 = 0.81%, October 2004–September 2006; Fisher and Larner 2007; and 2/175 = 1.14%, February 2009–February 2010; Menon and Larner 2011) and was maintained in later studies (8/140 = 5.7%; Ghadiri-Sani and Larner 2014; 38/246 = 15.4%; Cannon and Larner 2016; Table 1.5). Concerns over possible 6CIT overuse or misuse, which had been expressed locally, thus seemed to be without foundation. Indeed, more widespread use of 6CIT or other suitable CSI may be required to facilitate the aims of the Dementia CQUIN in closing the dementia diagnosis gap.

10.5.6 NICE Guidelines (2015): To Delay or Prevent Dementia Onset

NICE guidelines on delaying or preventing dementia—a worthy goal in light of the ongoing absence of disease-modifying therapy—were published in October 2015 (National Institute for Health and Care Excellence 2015). There were in all 15 recommendations delivered in two subsections: promoting healthy lifestyles (8) and service organisation and delivery (7). The headline recommendations were summarised as: stop smoking; be more physically active; reduce alcohol consumption; adopt a healthy diet; and achieve and/or maintain a healthy weight. Most controversial was the suggestion that no level of alcohol consumption was protective, as previously thought.

The guideline reads as a series of prescriptions and proscriptions for behaviour modification, an approach which has been described (Larner 2015a) as managerial or "Skinnerian", since it seems largely uninterested in the cognitive processes which cause people to fail to adopt, or indeed to do the opposite of, what promotes health. There seemed to be no expectation or plan to measure any impact of the guidelines.

10.6 Integrated Care Pathways (ICPs)

This book began by asking what contribution(s) to the diagnosis and care of people with cognitive disorders a neurology-led dementia clinic could make (see Introduction). The intervening sections have hopefully given some examples of potential contributions such a clinic can make. But services do not exist in isolation, so it is pertinent to ask where neurology-led dementia clinics might fit in with other services for patients with cognitive dysfunction.

A short answer might be "nowhere", this being an almost inescapable implication of the NICE/SCIE (2006) guidelines wherein neurologists were mentioned only once, a propos the initiation of cholinesterase inhibitor therapy (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence 2006:30). Of possible significance to this conclusion, however, was the fact that there was no input from a neurologist in the preparation of this document (Doran and Larner 2008). The National Dementia Strategy said a little more about neurologists (Larner 2009a), including the possibility that memory clinic services could be provided by neurologists (Department of Health 2008:77). Previously, a report on services for younger people with dementia published jointly by the Royal College of Psychiatrists and the Alzheimer's Society (2006) suggested that dedicated clinics may be required for the diagnosis of early-onset dementia and that such clinics might have a neurological lead.

Dementia is a multi-dimensional construct (American Psychiatric Association 2000) and a syndrome with variable age at onset and many possible causes (Larner 2008a, 2013a). Patient diagnosis may involve a wide array of professional groups in both primary and secondary care (e.g. Sect. 1.2). Hence it may be envisaged as a "boundary" condition which transcends traditional professional categories. The division between neurology and psychiatry is, after all, arbitrary (both deal with brain disorders) and hence it is not surprising that both neurological and psychiatric symptoms may occur in the same patient suffering from a single brain disease, although regrettably some diagnostic criteria for dementia disorders may neglect the psychiatric features (e.g. motor neurone disease: Sathasivam et al. 2008; prion disease: Zerr et al. 2009; Ali et al. 2013).

This interface between neurology and psychiatry has been a major focus of interest in the CFC (e.g. Larner and Doran 2002; Larner 2003b, 2006b, 2007d, 2008b, 2010e, 2013b; Doran and Larner 2004; Doran et al. 2006; Hancock and Larner 2008, 2009, 2015; Sathasivam et al. 2008; Abernethy Holland and Larner 2009; Fearn and Larner 2009; Wong et al. 2010; Ali et al. 2013; Bonello et al. 2014; Ziso et al. 2014; Randall et al. 2015; Williamson and Larner 2016). A "single point of

referral" (NICE/SCIE) or a "simple single focus of referrals from primary care" (NDS) may not therefore be entirely desirable. Diversity rather than uniformity may best serve patient needs in such a heterogeneous syndrome. The ideal model of service has not, to this author's knowledge, yet been defined.

If it be acknowledged that individuals with different generic skills may be involved in the assessment of patients with cognitive impairment and suspected dementia, the development of an integrated care pathway (ICP) may be an appropriate management strategy (Larner 2007e). ICPs aim to outline key diagnostic and therapeutic tasks and their timing for a condition or procedure, defined by specific inclusion and exclusion criteria (Kitchiner and Bundred 1996; Campbell et al. 1998) and facilitate the evaluation of process. Prior experience of developing an ICP for a "boundary" condition which transcends professional categories and involves more than one professional group in diagnosis and management (viz. idiopathic intracranial hypertension; Larner 2007f) was used to inform the development of a dementia ICP.

Most cases of dementia are of long duration, sometimes lasting for decades, with evolving symptomatology (neurological, psychiatric, functional, neurovegetative) and hence changing care needs. All these factors suggest that developing a meaningful ICP for dementia may be very difficult, let alone a test-treatment pathway (Ferrante di Ruffano et al. 2012; also known as phase IV diagnostic test accuracy studies: Larner 2015b:9,132–3), although some attempts have previously been made (e.g. Naidoo and Bullock 2001; Department of Health 2009:22). Any dementia ICP should accommodate the various interested disciplines, including old age psychiatry, psychiatry, geriatric medicine, and possibly clinical genetics and palliative care, as well as neurology (Box 10.2; Larner 2007e).

Patients who might reasonably be referred to a neurologist with specialist interest in dementia/cognitive disorders include those:

- ≤65 years of age.
- With neurological signs in addition to cognitive impairment, not deemed simply age-related (Sect. 3.2; Larner 2006d, 2012b, 2016:6–7), e.g.:

  Parkinsonism (raising the possibility of dementia with Lewy bodies, Parkinson's disease dementia, progressive supranuclear palsy, corticobasal degeneration, as well as AD).
  Myoclonus (prion disease, AD)
  Chorea (Huntington's disease)
  Muscle wasting +/− fasciculation (FTD/MND)
  Sensory complaints (prion disease, multiple sclerosis)

  In other words where there may be a suspicion of "secondary" dementia (Kurlan 2006).

- >65 years with family history of dementia suggesting autosomal dominant disease transmission (e.g. ≥3 affected family members in two generations with one person being a first-degree relative of the other two; Cruts et al. 1998; Goldman et al. 2005): for consideration of neurogenetic testing.

Box 10.2: Proposed integrated care pathway for dementia diagnosis (adapted from Larner 2007e)

Inclusion criteria:

- All patients presenting in primary care with complaint of memory impairment, preferably with informant corroboration.

Exclusion criteria:

- Patients with established aetiological diagnosis of dementia; generally should be referred directly to old age psychiatrists to access dementia care pathway, as per United Kingdom NICE/SCIE guidance, although there may be exceptions where specialised dedicated services exist (e.g. HIV dementia, Huntington's disease, prion disease, alcohol-related cognitive problems).

REFERRAL PATHWAY OPTIONS:
(A) Referral to old age psychiatrist:

- Elderly patients (>65 years)
- Monosymptomatic progressive impairment of episodic memory
- Absence of neurological signs, other than those appropriate to normal ageing
- ± behavioural and psychiatric symptoms of dementia (apathy, aggression)
- ± Impaired activities of daily living such that social and/or pastoral care in the community is required (as per NICE/SCIE).

(B) Referral to geriatrician, preferably with an interest in dementia:

- Elderly patients (>65 years)
- Comorbid pathology which may impact on cognitive function and requiring specific management

Once diagnosis of dementia is established, option to refer to old age psychiatry to access social care services as per NICE/SCIE.

(C) Referral to neurologist with specialist interest in dementia/cognitive disorders:

- Patients ≤65 years of age
- Patients of any age with family history of dementia suggesting autosomal dominant disease transmission
- Patients with neurological signs in addition to cognitive impairment and not appropriate to age, e.g. parkinsonism, myoclonus, chorea, muscle wasting ± fasciculation, sensory complaints, i.e. suspicion of secondary dementia

- Cognitive screening instrument administered, e.g. MACE, MoCA
- Informant collateral history plus assessment, e.g. AD8, IQCODE
- Morphological brain imaging (CT ± MRI)
- ± behavioural assessment (e.g. NPI, Cambridge Behavioural Inventory), functional assessment (e.g. IADL, DAD)
- ± Formal neuropsychological assessment by neuropsychologist (if diagnosis remains in doubt)
- ± functional brain imaging: SPECT, MR spectroscopy, amyloid PET
- ± diagnostic neurogenetic testing (may require input from clinical geneticist—see D)
- ± CSF analysis (Aβ42, total tau, phospho-tau)
- ± Brain biopsy
- ± other tissue biopsy (bone marrow, skin, rectum)

Once diagnosis of dementia is established, refer to young-onset dementia services where available, or old age psychiatry to access social care services as per NICE/SCIE.

(D) Referral to clinical geneticist:

- Any patient with a clinical phenotype and/or family history suggestive of a monogenic Mendelian disease (e.g. Huntington's disease) in whom diagnostic genetic testing is contemplated, for appropriate genetic counselling (see Sect. 7.3).
- Any patient with a family history of dementia suggesting autosomal dominant disease transmission (i.e. ≥3 affected family members in two generations with one person being a first-degree relative of the other two).
- Asymptomatic individuals ≤65 years of age with family history of dementia suggestive of autosomal dominant disease transmission (i.e. ≥3 affected family members in two generations with one person being a first-degree relative of the other two), or with a defined dementia-causing genetic mutation (e.g. presenilin-1, Huntington's disease) in immediate family member(s), who are contemplating or requesting predictive genetic testing, for appropriate genetic counselling.

(E) Referral to psychiatrist:

- Memory complaints associated with evidence or history of primary psychiatric disorder (depression, anxiety, schizophrenia) in the absence of other neurological symptoms and signs.

Developing ICPs for specific dementia diagnoses, such as the frontotemporal lobar degenerations (FTLDs), may be even more problematic than developing an ICP for dementia per se, in part because of the variable phenotype, encompassing either behavioural change or linguistic impairment (language fluency or comprehension) depending on whether the brunt of pathology falls within the frontal or temporal lobes, respectively. Although prototypical forms of FTLDs are relatively easily recognised by clinicians with experience of these conditions, diagnosis may often be challenging because of overlap of symptoms with the far more common condition of AD, with occasional misdiagnosis occurring (Davies and Larner 2009). The overlap between FTLDs and AD was reflected in older clinical diagnostic criteria (Varma et al. 1999). Delayed diagnosis of FTLD, even following contact with medical services, is common, with an average delay of nearly 3 years in a Scandinavian series, in which nearly three-quarters of patients initially received a non-dementia diagnosis (Rosness et al. 2008).

Neuropsychiatric symptoms are common in FTLDs (Mendez et al. 2008a; Box 10.3); symptoms which are incorporated in recent diagnostic criteria for behavioural variant FTD (Rascovsky et al. 2011). A sizeable proportion of FTLD referrals to CFC have come from psychiatry clinics (see Sect. 1.2.2). Psychosis is rare in FTLDs (Mendez et al. 2008b), with the possible exception of FTD/MND (Larner 2008b, 2013b), such that many of these patients are referred initially to psychiatry services, thereafter to neurology-led dementia clinics when features atypical for primary psychiatric disorders emerge (Larner 2007c, 2009b; Sathasivam et al. 2008; Ziso et al. 2014).

An ICP for FTLDs taking into account these problems has been proposed, based on empirical data from patients and their carers (Box 10.4; Davies and Larner 2010).

Once a diagnosis of dementia, and hopefully dementia subtype, has been established, patients may be referred on from neurology to young-onset dementia services where these are available or to old age psychiatry services to access appropriate pharmacotherapy and social care, as per NICE/SCIE (2006) recommendations. However, it is clear that for early diagnosis of dementia, neurologists with a special interest in the field should continue to have a role in the diagnostic phase of the dementia care pathway (Larner 2007c).

Box 10.3: Neurobehavioural features of FTLDs (after Mendez et al. 2008a)

Apathy-abulia
Disinhibition-impulsivity
Loss of insight
Decreased emotion, empathy
Violation of social/moral norms
Changes in dietary or eating behaviour
Repetitive behaviours

Box 10.4: Proposed integrated care pathway for frontotemporal dementia diagnosis (adapted from Davies and Larner 2010)

Inclusion criteria:

- All patients presenting in primary care and/or to psychiatry/old age psychiatry services with new, prominent neurobehavioural features (Box 10.3), based on history from a knowledgeable informant and corroborated by appropriate test instruments.

Exclusion criteria:

- Patients with an established alternative aetiological diagnosis of dementia, and/or monosymptomatic episodic memory impairment; such patients should be referred directly to old age psychiatrists to access dementia care pathway, as per United Kingdom NICE/SCIE guidance.

Referral to neurologist with specialist interest in dementia/cognitive disorders

1. Referral criteria:

- Patients ≤65 years of age.
- Patients with family history of dementia suggestive of autosomal dominant disease transmission (i.e. ≥3 affected family members in two generations with one person being a first-degree relative of the other two) since positive family history of dementia is more common in FTLD than AD.
- Patients with neurological signs suggestive of either frontal dysfunction ("frontal release signs", "primitive reflexes", e.g. pout, snout, grasp, palmomental reflexes) and/or anterior horn cell disease (cramps, muscle wasting especially around shoulder girdle, fasciculation).

2. Clinical diagnostic assessment:

- Cognitive assessment (e.g. MACE, MoCA).
- Behavioural assessment (e.g. Frontal Assessment Battery, Frontal Behavioural Inventory, Middelheim Frontality Index, FRONTIER Executive Screen).
- Functional assessment (Instrumental Activities of Daily Living Scale, Disability Assessment for Dementia).
- Collateral (caregiver) history: FLOPS, Iowa, IQCODE, CBI, AD8.

3. Investigation:

- Brain imaging: structural (CT, MRI), functional (SPECT, MRS, PET).

- EMG (even in absence of clinical fasciculation, to look for subclinical evidence of anterior horn cell disorder).
- ± EEG (typically normal in FTLDs, cf. AD).
- ± Neurogenetic testing if positive family history suggestive of autosomal dominant disease transmission, initially for tau, progranulin and C9orf72 gene mutations, or designated FTD panel.

4. Management:

- Provision of information to patient and carers about FTLDs.
- Referral to voluntary services (e.g. Alzheimer's Society, Pick's Disease Society).
- ± Referral to psychiatric services to manage neuropsychiatric symptoms.
- ± Randomisation to clinical trials.

10.7 Summary and Recommendations

Management of dementia is much more than simply pharmacotherapy although this is inevitably the sphere in which neurologists will be most involved. The liberalisation of guidance with respect to use of ChEIs and memantine (National Institute for Health and Clinical Excellence 2011) may have made these drugs more widely available (cf. Larner 2012a), and there seems no reason not to give all AD patients a trial of these medications unless there are compelling contraindications.

Addressing the information needs of patients and their carers is also of great and increasing relevance, a need which may be facilitated by contact with patient care organisations such as the Alzheimer's Society and signposting to selected information, for example materials accessible online. Use of integrated care pathways may facilitate diagnosis of dementia and integration of all appropriate service providers within the health care system, hopefully in a seamless manner. Implementation of national policies (the "top down" approach) may have outcomes unanticipated by their instigators, despite which clinicians will go about their work irrespective, guided by the training and expertise that they have acquired (the "bottom up" approach).

10.8 Concluding Thoughts

The foregoing chapters have hopefully demonstrated that neurologists are not redundant in the diagnosis and management of people with cognitive disorders, indeed have a valuable if circumscribed role to play. This clinical role may also facilitate research studies. However, it is not, and never was, the purpose of this book to be a merely factional account, a case of special pleading for the retention of neurology-led dementia clinics.

Whatever misgivings a neurologist may have about the National Dementia Strategy (NDS) for England as originally presented (Department of Health 2008, 2009; Larner 2009a), not least the anticipated changes in quality of life based on data from a single, 6-month, uncontrolled study (Banerjee et al. 2007), nevertheless the NDS authors were entirely correct to characterise their publications with the indefinite article ("a National Dementia Strategy"; Department of Health 2008, 2009) rather than the definite article (although it became *de facto* "the National Dementia Strategy"). Wittingly or not, this original appelation indicated that many other National Dementia Strategies were and are possible.

For example, one "National Dementia Strategy" might take the form of a campaign of vigorous primary and secondary prevention of dementia, by screening the whole adult population for recognised risk factors for dementia (e.g. vascular risk factors, especially hypertension; Patterson et al. 2008). Predicting dementia risk in 20 years time, based on factors such as age, education, blood pressure, cholesterol, and obesity (Kivipelto et al. 2006), might be an appropriate public health strategy, emphasizing a life-long, lifestyle approach to cognitive well-being ("brain health"; Lincoln et al. 2014). There is some preliminary evidence of falling overall prevalence and incidence of dementia in the UK but whether these reductions are a consequence of improved prevention and treatment of vascular risk factors, or due to other factors (e.g. better education, living conditions) is currently unknown (Matthews et al. 2016; Wu et al. 2016). Certainly a multidomain intervention targeting diet, exercise, and cognitive training as well as monitoring vascular risk factors has been reported to prevent cognitive decline in elderly at-risk people (Ngandu et al. 2015).

Another "National Dementia Strategy" might be based on genetic epidemiology, constructing "polygenic hazard scores" for the development of AD (Desikan et al. 2017; Larner and Bracewell 2017). Such "bioprediction" (Baum 2016), estimating individual differences in AD risk across a patient's lifetime, might be used at the individual level for the purpose of targeted screening or administration of preventative measures, as well as for future planning.

With predictions of dramatic increases in the number of dementia sufferers in the coming decades (e.g. Ferri et al. 2005; Alzheimer's Society 2007, 2014; Prince et al. 2015), prevalence continuing to increase even if incidence is falling because of the ageing of the population (Ahmadi-Abhari et al. 2017), another "National Dementia Strategy" or component thereof, might be to develop a dementia specialty *per se*, transcending current professional boundaries between neurology, psychiatry, geriatrics, etc. The skills required to diagnose and manage the dementia syndrome effectively require elements from all these disciplines, and potentially others as well (e.g. clinical genetics, palliative care). If management of the dementia care pathway from diagnosis to end-of-life care via a "single point of referral" for all cases (National Institute for Health and Clinical Excellence/Social Care Institute for Excellence 2006) is a legitimate goal, then specific training in dementia would seem to be legitimate, with all the implications of developing a faculty, training programmes, and certification to assure specific standards are met. The admixture of skills required for such a dementia specialist would perhaps make this a potentially attractive discipline to trainees.

Such an approach would perhaps return us to Alzheimer himself, neither a neurologist nor a psychiatrist, but a neuropsychiatrist of the German tradition (Larner 2006e). Ultimately the label is unimportant: what patients with dementia and their caregivers need are clinicians with the appropriate knowledge base, and supported by the appropriate resources, to ensure their concerns are appropriately addressed.

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