

Do we overtreat dementia?

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Abstract

The most frequent and devastating accompaniment of aging is dementia. Most manoeuvres aimed to improve the relentless decline in quality of the demented's life are based on relief of symptoms rather than an attack on causal mechanisms. Drugs for dementia provide only small measurable benefits for many patients. We should avoid the common clinical practice of overtreatment: prescribing one drug after another, or several drugs at the same time and numerous, often unsuccessful attempts to impede the dementing process.

If there is poor response or if side effects outweigh benefits, doctors should seriously consider the advantages of monitored withdrawal. These are not grounds for therapeutic nihilism because future treatments may halt or reverse the causal neurodegeneration.

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Commentary

Why do we strive relentlessly towards longevity? Recent literature, scientific, medical and philosophical is dominated by the desirability of prolonging life. This aim has become a routine that it is usually an unspoken assumption. Despite the anticipated pleasures of a long life, it is widely understood that the increasing life expectation of the 20th and 21st centuries is attended by many problems, many insoluble at the moment. Yet the pursuit of increasing survival continues, without thought about the consequences. In this quest the quality of life, the personal feelings of patient and family, which are often concealed, can be endangered to the point of neglect.

Experiments abound designed to unravel the fundamental cellular, ultracellular, genetic and immune abnormalities, which accompany aging in man and in laboratory animals, with the hope of reversing them. Many are important, showing

numerous mechanisms that relate to aging. But too often they indicate no more than an increased vulnerability to the aging processes or to particular dementing illnesses. No analysis or synthesis of data has yielded precise causal mechanisms that are reversible by therapy.

In man, vascular diseases, disabling degenerative joint diseases and the advent of various neoplasms add to the burdens accompanying normal aging. But the most frequent and devastating accompaniment of aging is dementia [1]. There are many causes, only a few potentially reversible. Dementia afflicts approximately 800 000 people in the UK and four million in the USA. Alzheimer's disease is the commonest cause that occurs in 60% patients, vascular dementia in 20% and diffuse Lewy body dementia in 15%. Mixed forms are also common.

But whatever their nature, symptoms and overwhelming social consequences for the demented person and his or her family prevail.

Many manoeuvres, mostly pharmacological and behavioural have been used to improve the relentless decline in quality of the dement's life. But most have been based on relief of symptoms rather than an attack on causal mechanisms Kozauer and Katz, reviewers at the American Food and Drug Administration, acknowledge "drugs for Alzheimer's disease, as a class, provide only the most questionable patient benefits." They warn that further loosening of the standard for drug approval will only encourage more new drugs that lack meaningful benefit and pose unnecessary risks [2]. Sadly none has had dramatic or consistent success and most new drugs have been clinically disappointing, failing to demonstrate efficacy in large, well-designed, phase 3 clinical trials of established dementia.

Although these are not grounds for therapeutic nihilism, clinical practice generally embraces numerous attempts to impede the process, too often without success. Most human treatments have been directed at relief of symptoms. Inhibitors of Serotonin reuptake, noradrenergic reuptake, Cholinesterase inhibitors (ChEIs): Donepezil, Galantamine, and Rivastigmine, the NMDA receptor antagonist Memantine, and other drugs are designed to slow deterioration in cognitive function [3] and are widely prescribed [4].

The National Institute for Health and Clinical Excellence (NICE) reported that ChEIs produced a consistent gain on cognitive and global scales compared to placebo in mild to moderate Alzheimer's disease [5]. The effects they said were small and there was little positive randomised evidence available on the long-term gain of ChEIs. There are however, doubts about the quality of evidence and the size of the benefits, which some say are minimal [6]. Drugs for Alzheimer's disease provide only the most questionable patient benefits [7,8].

The principal treatment for behavioural and psychological symptoms of dementia has been psychotropic medications; but these too have caused concern since they are associated with: increased cognitive decline, increased rate of stroke, Parkinsonism, cardiac arrhythmias and increased mortality [9]. Non-pharmacological treatments including cognitive behavioural therapy are in vogue,

but unlikely to be effective in moderate or severe dementia.

Future treatments may be directed at more fundamental mechanisms of neurodegeneration. For instance, in Alzheimer's disease the accumulation of amyloid β leads to amyloid β oligomerisation, tau hyperphosphorylation and aggregation, synaptic dysfunction, and neuronal death. Hyperphosphorylated, aggregated tau constitutes the intracellular filamentous inclusions that characterise many neurodegenerative diseases. Tau dysfunction is sufficient to cause neurodegeneration and dementia as shown by genetic studies. Both microtubule stabilisation, and neuronal precursor cells replacement have reduced tau pathology in a mouse model of human tauopathy [10].

Currently, overmedication is a common problem, especially in advanced dementia. Tjia and colleagues analysed data from 5,400 mostly bedridden patients with severe dementia. They found that more than a third received a cholinesterase inhibitor, while a quarter took memantine; 54 per cent of patients with severe dementia took at least one medication of questionable benefit [11]. These prescriptions, which were deemed unnecessary, cost almost \$300 per patient per month. It is clear that such overprescribing is commonplace, and that physicians often continue a longstanding regime without questioning its efficacy and side effects.

We should therefore exercise caution about the common habit of prescribing one drug after another, or several drugs at the same time. If there is poor response or if side effects outweigh benefits perceived by the patient, family or carers, the risks and benefits of stopping should be discussed fully with the patient (if possible), their family and carer. If there is doubt that a drug is doing more harm than good, graded, monitored withdrawal is indicated [4]. There comes a stage when the relentless progression of brain degeneration causes symptoms no longer amenable to drug treatment. Though hard to define that point exactly, the wise physician keeps that possibility in mind and acts accordingly.

Future treatments may halt or reverse neurodegeneration. They offer hope of more basic remedies in neurodegenerative diseases and dementia.

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