Depressive pseudodementia – how ‘pseudo’ is it really?

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Abstract: Depressive pseudodementia is a term commonly used to describe a condition whereby a patient experiences a cognitive deficit secondary to a primary mood disorder. This essay will explore whether depressive pseudodementia can truly be described as a dementia mimic or not. It argues that pseudodementia is closer in clinical nature to ‘true’ dementia, is not fully reversible, may act as a prodrome for ‘true’ dementia, and has an organic basis. All of these factors suggest that the term pseudodementia is misplaced, and the condition is more closely related to dementia than previously appreciated.

Introduction
Pseudodementia is a widely debated term in psychiatry, for which a consensus on definition is difficult to find. Most sources use it as a descriptive term for a cognitive deficit secondary to a primary psychiatric disturbance which mimics dementia, and which is reversible once the primary diagnosis has been treated. Such primary conditions include major depressive disorder, bipolar disorder, schizophrenia, and Ganser’s syndrome.

I will focus on depressive pseudodementia, resulting from a unipolar or bipolar affective disorder, which makes up the vast majority of pseudodementia described in the literature. I will explore whether we can consider depressive pseudodementia to be truly reversible, whether it acts as a risk factor or a prodrome for developing later dementia, and whether there are neuropathological changes which may explain the condition. I will then discuss the consequences of these findings, and address whether the term pseudodementia is outmoded.

Defining depressive pseudodementia
The term pseudodementia entered the psychiatric lexicon in 1961 with Kiloh’s landmark paper on the topic, but descriptions of the condition are found much earlier [1]. Albert Mariet (1852-1935), Professor of Mental Illness in the University of Montpellier published Démence Mélancholique (his treatise on ‘melancholic dementia’) in 1883 [2]. Since then, there has been a steady interest in the topic, particularly in the past decade owing to the widespread use of imaging techniques which have enabled us to seek an organic substrate for the condition.

Kiloh’s paper emphasised that the term should not be used diagnostically, just descriptively; he saw it as hugely important to identify patients with reversible causes of cognitive impairment, so they are not confined to the “therapeutic nihilism” of being labelled with an irreversible untreatable disease [3]. His criteria were as follows:

(i) pseudodementia is an intellectual impairment in a patient with a psychiatric disorder;
(ii) the intellectual deficit is reversible;
(iii) the features resemble those of a neuropathologically induced cognitive deficit;
(iv) there is no apparent underlying neuropathological process.

The difficulty in defining pseudodementia relates to the polemic surrounding its exact nature. The word itself implies that the cognitive deficit is not a ‘true’ dementia, which is defined by the Diagnostic and Statistical Manual 4th Edition of the American Psychiatric Association (DSM-IV) as being ‘the development of multiple cognitive deficits (including memory...
impairment) that are due to [an organic cause]’ [4]. DSM-IV mentions pseudodementia fleetingly in the context of distinguishing dementia from a major depressive episode using a patient’s premorbid state, stating that if there is a long history of premorbid cognitive decline dementia is more likely, as opposed to a sudden decline associated with depression which is more likely to be a pseudodementia.

Kiloh’s criteria somewhat distance pseudodementia from the DSM-IV definition of dementia. Yet several studies have shown that features we consider in the realm of dementia – irreversibility, progression and neuropathological changes – are also found in patients with depressive pseudodementia.

**Nature of pseudodementia**

In 1979, Wells described what he saw as the key differences in presentation between pseudodementia and dementia [5]. Features more consistent with pseudodementia than organic dementia included a precise onset, rapid deterioration, relatively good attention and concentration, patchy memory loss, and minimal patient effort to cope with the dysfunction. He was quite clear that pseudodementia ‘caricatures’ rather than ‘mimics’ dementia, and that his criteria could be used to distinguish clinically between the conditions.

Yet in practice it is not that simple to establish a definitive diagnosis. Many features overlap, and the complex relationship between depression and dementia and their frequent coexistence in the older population makes it hard to discern which the primary diagnosis is. This confusion is also found in the literature. Tobe describes a case report highlighting just how difficult it is to disentangle the diagnoses of depression and dementia, in particular when confounded with polypharmacy, and in this case, differing views and lack of collaboration between clinicians [6].

All in all, it is fair to say that though Wells’ criteria may have helped distinguish pseudodementia from dementia in his patient set, the differences between pseudodementia and dementia are not that well demarcated.

**Is it reversible?**

Classically one of the major distinguishing features between dementia and pseudodementia is that of reversibility. Depressive pseudodementia is considered to be a key reversible form of cognitive deficit, whereby if the affective disorder at play is treated, so is the dementia [7]. Nonetheless, a lot of evidence would suggest that even once a patient’s mood has been stabilised the patient may still have residual cognitive impairment, albeit with less impairment than during the period of pseudodementia. We will examine a selection here.

Saez-Fonseca looked into the long-term consequences of depressive pseudodementia [8]. As well as finding a fourfold increase in relative risk for developing dementia in the years following the episode of pseudodementia (discussed below), it was interesting to note that the Mini Mental State Examination (MMSE) score was still significantly lower in the ‘reversible’ cognitive impairment group after treatment compared to the group of non-cognitively impaired depressed patients. This suggests there is still residual cognitive impairment in the pseudodementia group, and thus it is not fully reversible. The mean Geriatric Depression Scale (GDS) score after treatment was significantly higher in the pseudodementia group too; the authors interpreted this as patients with pseudodementia having depression more resistant to treatment, but even if this the case we are unable to tell from this study whether, if the GDS score fully returned to normal, the MMSE would also return fully to baseline.

A 2013 study used electroconvulsive therapy (ECT) to treat 20 patients with depressive pseudodementia, and found that it resolved both symptoms of depression and dementia [9].
Vast improvements in MMSE and depression scores were seen, although notably over half (11/20) patients still had an MMSE score of below 27/30 (considered to be the cut-off for normal cognition) after 8 weeks of treatment, despite their mood post-treatment returning to within normal range according to the Hamilton Rating Scale for Depression (HRSD).

Altogether, although pseudodementia is classically considered a reversible form of cognitive impairment, evidence would suggest that this is not necessarily the case.

**Prodrome or risk factor ... or both?**

One of the key debates in the field of depressive pseudodementia is whether depressive episodes, with or without coexisting cognitive impairment, either act as an independent risk factor for the development of dementia later in life, or represent a prodromal state to the dementia. The difference is based partly on the time interval between the onset of depression and the onset of dementia (an association significantly before the onset of dementia would imply depression being a risk factor rather than a prodrome), as well as whether there is a period free of cognitive impairment between the depressive episode and the onset of dementia (if not, that would imply a prodrome).

The case for depressive symptoms being a prodrome for dementia has been widely made, for example in one key community based prospective study by Chen, which found that depressive symptoms were prodromal to dementia rather than predictive of it [10]. Schweitzer reviewed the evidence and concluded that the epidemiological data support depression as a prodrome for both Alzheimer’s disease and vascular dementia, but there is still controversy as to whether it is a true independent risk factor [11]. Confusion arises as to the huge heterogeneity of study types that have been used to examine the relationship. Though the study population did not have cognitive testing done during the depressive episode to confirm pseudodementia, Bhalla found a twice increased risk of mild cognitive impairment immediately after resolution of depressive symptoms in patients diagnosed with late life depression, suggesting the depression and cognitive impairment may be part of the same disease process [12].

On the other hand, one meta-analysis containing 20 studies and over 100,000 subjects reported that depression doubled the risk of developing dementia later in life [13]. The authors suggested depressive episodes acted as an independent risk factor rather than a prodrome (though they do not rule out both being a possibility) as the interval between diagnoses is positively and significantly correlated with risk of developing Alzheimer’s disease. This agreed with another key study in the field, which found that, though the relationship was strongest when onset of depression was closer in time to onset of dementia, the strength of the relationship over one year and even over 25 years apart suggested that it was unlikely to just be a prodrome, but also an independent risk factor [14].

Kessing and Anderson performed a very large longitudinal study (22,974 patients) over 29 years from 1970 to 1999 looking at whether prior admissions to a psychiatric ward for depressive disorder or bipolar disorder were related to subsequent readmission for dementia [15]. It reported that the rate of dementia increased by 13% for every episode leading to admission for depressive disorder, and 6% for bipolar disorder. Although this study did not look at pseudodementia specifically, and may have underestimated dementia diagnosed elsewhere than on a psychiatric ward, it was a powerful study and lends weight to the theory that depression is a risk factor for dementia later in life. In addition, Saez-Fonseca reported a relative risk of nearly 4 for patients admitted for depression who presented with pseudodementia, compared with those who were cognitively intact, for developing dementia at follow up 5-7 years later [8].
Perhaps the distinction between prodrome and risk factor is a false one: late life depression could be both a prodrome and a risk factor for dementia; they need not be mutually exclusive [16]. Kasahara built six models into which cases in the literature fall; three where depressive episodes precede the dementia by some time (more in keeping with depression as a risk factor), one of which includes a period of pseudodementia during the depressive phase, and three where depression is a precursor symptom, an initial symptom, or it just appears during the course of the dementia [17].

Kobayashi and Kato propose that pseudodementia and depression in Alzheimer’s disease lie on a spectrum from depression without dementia to dementia without depression [18]. They established this in the context of Janet’s concept of ‘psychological tension’, whereby depression lowers psychological tension revealing latent dementia. They named the concept the ‘depression-dementia medius’ [19]. They saw pseudodementia as a revelation of latent dementia in depressive illness, and go as far as suggesting that treatments useful for depressive symptoms may be useful in treating those with dementia even if they do not exhibit depressive symptoms simply by reducing psychological tension (for example, by providing a reassuring environment, prescribing antidepressants, using music and reminiscence therapies, or even ECT).

So what can we draw from this? The evidence that depression acts as a risk factor for dementia is fascinating, and stresses even further the importance of prevention and early treatment of mood disorders, especially later in life. Yet the studies that suggest it may be a prodrome are particularly relevant to our discussion, as it adds a new dimension to the pseudodementia debate – could depressive pseudodementia sit somewhere within this disease process linking late life depression and dementia? We may be seeing evidence that pseudodementia is anything but ‘pseudo’, but actually a precursor to ‘true’ dementia. Regarding implications for current services, this highlights one of the issues with having memory clinics separate from community mental health teams with little interaction, in that if depression and dementia are so intrinsically linked, addressing them separately may not be providing optimum care for patients.

**Proposed biological mechanisms for depressive pseudodementia**

The biological mechanism of pseudodementia and the organic links between depression and dementia merit exploration. In the 19th century Marriet observed that there were changes to the temporal lobe post mortem in patients with depression [2]. His small series of relatively young patients (21 cases with a mean age of 41 years) nonetheless showed no significant difference in overall extent and nature of depressive symptoms and cognitive deficit when compared to a ‘current’ series of patients with pseudodementia from 1985. Marriet believed melancholic dementia to be organic in nature, due to the temporal relationship between the melancholia and the ‘weakening of the intelligence’. Several studies have since suggested organic changes in patients with pseudodementia, although sometimes the areas involved differ slightly from those involved in classical dementias.

Dolan performed positron emission tomography (PET) scans of patients with major depressive disorder and reversible cognitive impairment, and found blood flow abnormalities in anatomical areas additional to those seen in depression and distinct from those seen in neurodegenerative dementia (namely decreases in the left anterior medial prefrontal cortex (PFC) and increases in the cerebellar vermis) [20]. Though the authors caution against using their techniques clinically to differentiate between ‘organic’ dementia and depressive pseudodementia, they claim that they demonstrate an anatomical role for the PFC and vermis in depressive pseudodementia.
Caine reviewed the evidence of memory testing in depressive pseudodementia patients and found that patients with depressive pseudodementia exhibit a ‘subcortical’ pattern of memory loss, with patterns of cognitive impairment being similar to patients with subcortical dementias such as Huntington’s Disease (except for the learning of new information, in which depressive pseudodementia patients perform significantly better) [21]. A later study by Massmann corroborates this, finding that patterns of memory loss determined using the California Verbal Learning Test (CVLT) in patients with depressive pseudodementia are more similar to patients with subcortical dementia than with cortical dementia [22].

Butters suggested various biological substrates as to how the link between depression and cognitive impairment could be mediated [16]. Hippocampal volume loss might result from impaired hypothalamic-pituitary-adrenal central drive in depression, leading to chronically elevated glucocorticoid levels and resultant hippocampal neural damage. Also, cerebrovascular disease and Alzheimer’s disease pathology may interact to cause frontostriatal damage and hippocampal volume loss, causing simultaneous depression and mild cognitive impairment (MCI) which then progresses over time to Alzheimer’s disease or vascular dementia. Other sources propose that the high prevalence of deep white matter lesions found in various brain imaging studies of patients with depression might link it aetiologically to vascular dementia [11].

Overall, though there are no conclusive findings as to the nature and location of anatomical changes in depressive pseudodementia, the likelihood is that they are there, and may be quite similar in nature to the changes found in several types of dementia. This again would contribute to the argument that pseudodementia is more akin to dementia than it is currently credited with.

**Conclusion – is pseudodementia an appropriate term?**

It seems that, based on work in the field to date, depressive pseudodementia may be closer to ‘true’ dementia than previously considered. An array of evidence suggests that pseudodementia is often difficult to distinguish from dementia clinically, it may not be entirely reversible, it may act as a prodrome to dementia, and it may have an organic basis with structural brain changes. Thus, we must pose the question: is pseudodementia truly ‘pseudo’? And if not, should the term pseudodementia be dropped altogether as misleading and inaccurate?

I would argue that the evidence presented in this essay suggests that pseudodementia shares enough features with organic dementia for the prefix ‘pseudo’ to be erroneous. Snowdon’s review of Kiloh’s landmark paper suggests that only the few cases with truly reversible dementia and no lasting cognitive impairment can be called pseudodementia, and if there are organic changes in pseudodementia the prefix is misplaced [3]. However, he does conclude that the term is still useful in instigating debate into the aetiology behind a particular patient’s cognitive impairment.

In terms of renaming the condition, Reifler suggests that pseudodementia might best be renamed predementia, due to the weight of evidence suggesting it acts as a prodrome to dementia [23]. Perhaps even ‘pseudopseudodementia’, though unwieldy, would be more accurate for the majority of cases of pseudodementia which have an organic basis and are not fully reversible.

Whichever term we use to describe the condition, it remains that depressive pseudodementia is of considerable relevance. Mood disorders are a major issue in old age psychiatry, and the complex relationship between mood disturbance and cognitive impairment is gradually becoming elucidated. It would be fair to say not enough research has yet explicitly focussed...
on whether pseudodementia is a different entity in all of the respects explored, and a clear judgement on how pseudodementia should be considered clinically should be reserved until this is carried out. A deeper understanding of the phenomenon of depressive pseudodementia would help clinicians best treat the condition and allow for more accurate prognoses to be formed.

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References

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