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The new DSM-5 diagnosis of mild neurocognitive disorder and its relation to research in mild cognitive impairment

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The Diagnostic Statistical Manual-5 (DSM-5) has included a category named the neurocognitive disorder which was formally known in DSM-IV as 'dementia, delirium, amnestic, and other cognitive disorders'. The DSM-5 distinguishes between 'mild' and 'major' neurocognitive disorders. Major neurocognitive disorder replaces the DSM-IV's term 'dementia or other debilitating conditions'. A pivotal addition is 'mild neurocognitive disorder (mNCD)' defined by a noticeable decrement in cognitive functioning that goes beyond normal changes seen in aging. It is a disorder that may progress to dementia – importantly, it may not.

Presently, our understanding of mNCD is derived from research on mild cognitive impairment (MCI). Whereas there is currently no clear treatment for mNCD, many experimental therapies now and into the future will focus upon secondary prevention, namely decreasing the risk of progression to major NCD. In this article, we will focus on mNCD by reviewing the relevant literature on MCI. We will review the research on the incidence and prevalence of MCI, conversion rates from MCI to dementia, risk factors for conversion of MCI to dementia, comorbidity of MCI with other neuropsychiatric disorders (NPS), and the development of treatment strategies for neuropsychiatric disorders in MCI.

The presence of NPS is common among individuals with MCI and is an important risk for progression to dementia. However, there has been little research on effective treatments for NPS in MCI. Clinicians and investigators must determine if the treatment of the NPS in mNCD will improve quality of life and help reduce the progression of the cognitive impairment.

Keywords: mild cognitive impairment; psychological and behavioural symptoms; screening and diagnosis

Introduction

The recently published DSM-5 (American Psychiatric Association [APA], 2013) includes a subsection entitled neurocognitive disorders (NCDs) which replaces the Diagnostic and Statistical Manual-IV (DSM-IV) TR (APA, 2000) category of delirium, dementia, and amnestic and other cognitive disorders category. The DSM-5 distinguishes between 'mild' and 'major' NCDs. The diagnosis of major NCD replaces the DSM-IV's term 'dementia or other debilitating conditions'. However, a pivotal addition is the new diagnosis of 'mild neurocognitive disorder' (mNCD). It is a disorder that may progress to dementia – importantly, it may not.

Blazer (Blazer, 2013) recently summarized the most salient benefits of this new diagnosis:

(1) The diagnoses of mNCDs reflect an emerging literature that confirms both the improvement in early diagnostic techniques and the recognition of the neuropathology underlying these disorders emerge well before the onset of clinical symptoms seen in dementia.
(2) The importance of identifying this population for research in order to focus on slowing progression.
(3) The patient's need for and seeking of assistance in dealing with the initial onset of such problems, and potential need to make plans for the future.
(4) 'Once a treatment is available that may slow down, stop or even reverse the course of the NCD, the time for intervention will be early in the development of the disease (e.g., mNCD), whatever the etiology'.

Moreover, it should be additionally noted that with the potential development of biomarkers and genetic testing for specific types of dementia (e.g., Alzheimer's disease (AD)), interventions may even be started before the onset of symptoms.

In addition to the new diagnoses of mNCD, other substantial changes to this DSM-5 category included criteria related to the preferable use of objective neurocognitive assessment in diagnosing individuals with mNCD. Although DSM-5 does not identify the specific neurocognitive assessment to be used, it is noted that the deficit on a given test would be expected to be between 1 and 2 standard deviations below normal. Additionally, in the DSM-5 text, there is the removal of memory impairment as an essential criterion and improved specification of behavioral symptoms associated with cognitive impairment. Whereas in the DSM-IV TR, the domains of dysfunction addressed memory impairment, aphasia, apraxia, agnosia and executive dysfunction, the DSM-5 focuses more broadly to include complex attention, executive function,

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learning and memory, language, perceptual-motor, and social cognition.

Mild neurocognitive disorder

The DSM-5 diagnosis of mNCD is defined by a noticeable decrement in cognitive functioning from a previous level and requires the person to be engaging in compensatory strategies and accommodations to maintain independence and perform activities of daily living. However, for the most part, mNCD does not interfere with independence. Mild neurocognitive decline *may* signal the subsequence occurrence of more severe decline (e.g., major NCD); however, that is not necessarily the case. The mNCD diagnosis represents a heterogeneous category, encompassing multiple possible etiologies (e.g., prodromal AD and acquired stable cognitive deficits associated with traumatic brain injury (TBI)).

Presently, the etiologies for major NCD (but not mNCD), when known, are to be coded as subtypes. Subtypes include AD, Lewy-body disease (LBD), frontotemporal dementia, vascular neurocognitive impairment, TBI, HIV, Huntington's disease, and Other causes. In progressive neurodegenerative disorders and some forms of vascular cognitive impairment, minor and major NCD may be earlier and later stages of the same disorder. However, importantly the etiologies for mNCD are not coded in DSM-5 – given the uncertainty of the link. During the development of DSM-5, this was a much discussed issue. As future biomarkers are identified in upcoming iterations of the DSM-5, etiologies will likely be specified within mNCD. Research in mNCD must move to further refine definitions and subtypes based on etiology, prognosis, and treatment.

Definitions of mild cognitive impairment

Presently, our understanding of mNCD is derived almost exclusively from research in mild cognitive impairment (MCI). The definition of MCI according to the National Institute on Aging-Alzheimer's Association (NIA/AA) workgroups diagnosis guidelines for AD (Albert et al., 2011) includes a change in cognition reported by the patient, client, or clinician, objective evidence of impairment in one or more domains, preservation in functional abilities, and not demented. The DSM-5 workgroup on NCDs (Ganguli et al., 2011) identified some distinctions between mNCD and MCI as outlined in the NIA/AA. They noted that mNCD encompasses a more diverse group of entities including mild acquired impairments in younger individuals and impairments that may be transient, static, or even reversible.

Other researchers have used various terms to describe cognition that lies between normal cognitive aging and dementia (see Geda & Nedelska, 2012; Panza et al., 2005). In amnesic MCI (aMCI), memory is the dominant problem. aMCI is most often thought of as a prodrome to AD (Petersen & Morris, 2005). There are also non-amnestic types of MCI (Asada et al., 1996); for example, cognitive impairment–no dementia (Arthur, 1973; Ebly, Parhad, Hogan, & Fung, 1994) emphasizes cognitive impairment other than memory. However, for the diagnosis of mNCD, the DSM-5 does not differentiate between aMCI and non-amnesic MCI (naMCI). There is also multiple-domain MCI in which memory and other cognitive domains are impaired. Patients with multiple-domain MCI may be at a higher risk of conversion to dementia (Crocco & Loewenstein, 2005). There are MCI subtypes based on presumed etiology (e.g., MCI-AD, vascular MCI, or MCI–LBD). However, as noted earlier, at this time such subtypes are not formally specified or coded in mNCD in the DSM-5. These subtypes are, however, coded for in major NCD in the DSM-5.

Research in the area of MCI is what informs us today on how to proceed in terms of diagnosis, research, and treatment for mNCD.

Prevalence of MCI

There has been a prolific body of research on MCI over the last decade (Petersen et al., 2009). However, definitions of MCI have varied (Panza et al., 2005) resulting in inconsistencies across findings (Aschoff, Hoffman, Pohl, & Wever, 1975; Petersen et al., 2001). Future research needs to apply diagnostic criteria for mNCD consistently in order to better estimate prevalence. Petersen and Morris (2005) outlined the main sources of variability in research on MCI: (1) criteria for MCI, (2) implementation of the criteria, (3) source of subjects, and (4) reference standards for normal performance. Preliminary data from reliability studies on the DSM-5 for mNCD suggests that there is a clear improvement in inter-rater reliability among clinician when the new DSM-5 criteria for mNCD are applied along with the use of standardized testing (Dan G. Blazer, personal communication, March 24, 2014).

Researchers have examined prevalence rates of MCI across varied definitions (for a review see Panza et al. (2005)). In a recent study, Ward, Arrighi, Michels, and Cedarbaum (2012) reported substantial variation in rates of prevalence and incidence associated with varied definitions (MCI: 21.5–71.3; aMCI: 8.5–25.9 per 1000 person-years) and prevalence (MCI 3%–42%; aMCI 0.5%–31.9%).

In a community sample of older adults in the Bronx ($N = 1944$), researchers (Katz et al., 2012) found 21.5% of the sample with prevalent aMCI or naMCI at baseline. The incidence of aMCI was 3.8 and for naMCI, it was 3.9 per 100 person-years. They found little difference in men and women but found lower rates in whites than in blacks (19.1% vs. 27.3%). Sex, education, and race were not significant risk factors for incident aMCI. In contrast, Panza et al. (2005) commented that the incidence rates of all predementia syndromes are higher in subjects with less education, but education is not consistently related to prevalence rates. Other studies have found lower education to be predictive of cognitive decline (Sachs-Ericsson & Blazer, 2005). Additionally, in the Bronx study (Katz et al., 2012), elderly black individuals appear to be at increased risk for naMCI which may be related to higher rates of cerebrovascular disease and cardiovascular risk

factors among African-Americans compared with whites (Katz et al., 2012). Importantly, the authors note that there is a paucity of longitudinal research on MCI. Future research in this area, using carefully applied diagnostic criteria for mNCD, is clearly needed to document the incidence and prevalence of the DSM-5-defined mNCD.

Conversion of MCI to dementia

Rates of conversion from MCI to dementia vary greatly across definitions (see Panza et al., 2005) and setting. Rates tend to be higher where individuals sought treatment compared to general population settings; individuals with more severe symptoms are likely more motivated to seek treatment in a memory disorder clinic (Crocco & Loewenstein, 2005). Mitchell and Shiri-Feshki (2009) found, in specialty settings, rates of conversion from MCI to dementia to be 39.2%, and in general population samples, to be 21.9%. In one review (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003), rates of conversion to dementia over 2.6 years ranged from 23% to 47%. Importantly, the majority of individuals with MCI do not progress to dementia during the follow-up period of most field studies.

There has been an attempt to identify the progression of decline by MCI subtype (Panza et al., 2005). In a recent study (Espinosa et al., 2013), data from 550 MCI patients was analyzed based on Petersen's criteria for MCI (2004). The probable aMCI subset of patients had 8.5 times higher risk of converting to dementia compared to the probable naMCI group. Probable amnesic has been associated with prodromal AD.

Researchers are identifying neurological tests that are sensitive to detecting individual who are more likely to convert (Egli et al., 2014). Researchers are also attempting to identify biosignatures for conversion (e.g., neuroimaging, demographic, genetic, and cognitive measures) (Eskildsen et al., 2013; Torosyan, Dahlbom, Czernin, Phelps, & Silverman, 2013; Ye et al., 2012).

Reversion from MCI to normal

Some individuals diagnosed with MCI revert to normal cognitive functioning. In a recent study, Roberts et al. (2014) examined a clinical sample of individuals with MCI. They identified characteristics associated with reversal to normal cognition. These factors included being married, having non-amnestic impairment or single-domain MCI, having no apolipoprotein E (APOE) $\epsilon 4$ alleles, having better everyday functioning, and higher scores on cognitive tests. Similarly, in a sample of clinical patients diagnosed with MCI (Arean, Peri, & Nezu, 1993), approximately 16% reverted back to normal at one year, characteristics associated with reversion to normal included better cognitive scores, better functioning, and absence of the APOE $\epsilon 4$ allele.

In another recent study, reversion to normal was characterized by higher complex mental activity, greater openness to experience, better vision, better olfactory ability, or larger combined volume of the left hippocampus and left amygdala. Reversion to normal was also associated with a larger drop in diastolic blood pressure between baseline and follow-up (Crawford et al., 2013). However, for the most part, studies have not documented what the apparent cause was for the initial MCI diagnosis that subsequently remitted. There are a number of possibilities. For example, they may have been depressed, medically ill, or there may have been measurement error in the initial assessment or post assessment. Nonetheless, studies suggest that those with documented MCI who reverted back to normal were at a significantly higher risk for future cognitive decline (Arborelius, Owens, Plotsky, & Nemeroff, 1999; Roberts et al., 2014).

Research identifying risk factors for the conversion of mNCD to major NCD will become of greater importance as treatments for mNCD are identified. One important area of investigation is the role of neuropsychiatric symptoms (NPS) in MCI. Indeed, an important risk factor in progression of MCI to dementia is the presence of NPS. First, it should be noted (and briefly reviewed below) that neuropsychiatric symptoms in older adults, without MCI, are associated with increased risk in the development of cognitive decline, in particular the presence of symptoms of depression.

Depression as a risk for MCI and dementia

Depression has been found to be associated with an increased risk for MCI, dementia, and AD (Saczynski et al., 2010). There is growing body of research suggesting that depression may influence the onset and course of cognitive decline. For example, in one study, depressive symptoms at baseline were associated with increased risk of MCI; specifically, 10.0%, 13.3%, and 19.7% for those with no, low, and moderate or high depressive symptoms, respectively (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006). In a recent quantitative meta-analysis, depression was a major risk factor for incidence of MCI and dementia (Gao et al., 2013).

Depression may be a risk factor for cognitive decline (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006; Zeki Al Hazzouri et al., 2014), cognitive decline may be a risk factor for depression (Richard et al., 2013), and/or there may be a third variable (such as a neurological event) that causes both depressive symptoms and cognitive decline. These hypotheses are not mutually exclusive (Jorm, 2000; Jorm, 2001; Ownby et al., 2006; Sachs-Ericsson, Joiner, Plant, & Blazer, 2005).

In their review, Byers and Yaffe (2011) summarize the likely biological mechanisms linking depression to dementia as including vascular disease, alterations in glucocorticoid steroid levels and hippocampal atrophy, increased deposition of amyloid-β plaques, inflammatory changes, and deficits of nerve growth factors. Age of onset of depression may be associated with different causal mechanisms linking depression and cognitive decline (Sachs-Ericsson et al., 2013). The association between early onset depression (onset before age 60) and cognitive decline may be best understood as implicating

glucocorticoid functioning (Sapolsky, 2001). In contrast, late onset depression (LOD, occurring after age 60) has been associated with more severe cognitive decline and neurological changes indicative of a more prominent biological pathology (Hickie et al., 2005; McKinney & Sibille, 2013; Sachs-Ericsson et al., 2013). In LOD, neurological changes are posited to give rise to both cognitive deficits and depressive symptoms (Paranthaman et al., 2012) or LOD may be a prodromal expression of AD (Dillon et al., 2009).

One review (Leonard, 2007) suggests that depression is associated with inflammation that could precipitate neurodegenerative changes associated with AD and other dementias. The depression may not be always causal but may exacerbate preexisting cognitive impairment by depleting cognitive reserve (Jorm, 2001). If the depression is treated successfully, then the MCI improves, but the individual may be at greater risk for AD (Alexopoulos, 2005). When making a diagnosis of mNCD, the Criteria D in the DSM-5 specifies that 'the cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)'. In making diagnosis, this possibility must be carefully evaluated.

In this regard, it should be noted that cognitive impairment may be a symptom (that will remit) in older adults with depression. Pseudodementia is a syndrome in which dementia is mimicked; however, the underlying cause is a psychiatric disorder which is typically, but not always, depression (Sachs-Ericsson & Blazer, 2006). A meta-analysis has shown that depression is associated with broad impairments on neuropsychological measures of executive function (Snyder, 2013). Studies suggest that different antidepressant agents may improve cognitive functions in patients with major depressive disorders (Herrera-Guzman et al., 2009). In one study (Ramakers et al., 2010), researchers found that in the absence of moderately severe memory impairment, depression is more likely to be associated with primary depression than with prodromal AD.

Depression in late life can result from a number of neurodegenerative conditions associated with aging and cerebrovascular disease. There are several vascular risk factors associated with an elevated risk of incident MCI (Ganguli, Fu, Snitz, Hughes, & Chang, 2013). The vascular depression hypothesis (Alexopoulos, 2006) postulated that cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults. Frontal-subcortical pathways affected by vascular disease are also involved in mood regulation (Alexopoulos et al., 1997; Krishnan, Hays, & Blazer, 1997). McKinney and Sibille (2013) proposed that late-life depression is the integrated output of biological processes with age-dependent gene expression being the mechanism driving dysfunction in multiple biological pathways.

Does treatment of depression lower risk for subsequent cognitive decline?

Executive dysfunction and information processing speed deficits are often considered to be hallmark cognitive features of late-life depression. In a study (Mackin et al., 2013) investigating the impact of psychotherapy (problem-solving therapy and supportive therapy) on cognitive functioning in older adults with late-life depression and executive dysfunction, there were clear improvement in measures of executive functioning (regardless of therapy type) but not for other measures of cognitive functioning. Further improvements were associated with decreased depressive symptom.

It has been suggested that long-term treatment with antidepressants in older adults with depression may decrease the risk of developing some types of dementia, depending on the type of depressive disorder (Kessing, 2012). Antidepressant medication may have an impact on the neurodegenerative processes associated with depression (Leonard, 2007).

Animal models have shown that antidepressant medications (Malberg, Eisch, Nestler, & Duman, 2000; Santarelli et al., 2003) are associated with the repair of neuronal networks (Sairanen, Lucas, Ernfors, Castrén, & Castrén, 2005) and enhance axonal and dendritic sprouting (Fujioka, Fujioka, & Duman, 2004; Vaidya, Siuciak, Du, & Duman, 1999). In one study of depressed patients (Kessing, Forman, & Andersen, 2011), long-term treatment with the older antidepressants (e.g., tricyclics) was associated with a reduced rate of subsequent dementia, whereas treatment with other kinds of antidepressants (e.g., SSRI) was not. However, it should be noted (as will be described below) that this is not the case for treating depression in individuals with dementia; anticholinergic effects of the tricyclics may worsen cognition.

However, this is a difficult area to explore because data is often retrospective and patients with depression are not typically 'randomly assigned' to treatment. Thus, it is difficult to surmise the extent to which different pharmacological treatment modalities and types of antidepressants potentially lower dementia risk in patients with depression. As suggested by Byers and Yaffe (2011), it is critically important to determine if treatment of depression would delay or prevent dementia.

Whereas symptoms of depression may signal an increased risk for cognitive decline in older adults, the presence of NPS among individuals with MCI has been shown to increase risk for the progression of MCI to dementia. Additionally, NPS are prevalent among individuals with MCI, although these individuals often present to clinicians with the primary complaint of some problems with their memory and/or functioning.

Prevalence of neuropsychiatric symptoms in MCI

There is a high comorbidity of NPS in MCI. It should be noted that in the DSM-5 diagnosis of mild and major NCD, there is a further classification used to identify behavioral symptoms. These include: psychosis, mood disturbance, apathy, agitation, and with other behavioral disturbance. In a review of studies on the prevalence of NPS in MCI (Apostolova & Cummings, 2008), there was considerable variability depending on definitions and methodology used. They reported that neuropsychiatric

manifestations occur in 35%−75% of patients with MCI. Frequently associated neuropsychiatric disturbances include apathy, depression, and agitation and/or aggression (Lyketsos et al., 2002).

Depressive symptoms are common for older adults with MCI. Panza et al. (2010) estimated that the prevalence of depression in individuals with MCI was higher in hospital-based studies (median = 44.3%) than in population-based studies (median = 15.7%). Rosenberg et al. (2011) examined NPS in MCI and found prevalence for symptoms as follows: depression 27.3%, apathy 16%, and irritability, 25%. Rosenberg et al. (2011) examined NPS in MCI by subtypes. No differences were observed in the prevalence of NPS between aMCI and naMCI. However, the presence of executive dysfunction predicted greater severity and/or prevalence of certain NPS. They concluded that it is possible that executive dysfunction with an NPS profile is associated with prodromal AD and might constitute a subtype of prodromal AD with implications for prognosis and treatment.

Researchers have generally found that there is a progressive increase in the number of NPS from normal to MCI to dementia (Crocco & Loewenstein, 2005; Geda et al., 2004). The presence of NPS may be a marker of MCI severity (Feldman et al., 2004), which may in part explain the association of NPS with progression to dementia. Not only is depression in MCI associated with a higher rate of conversion to dementia, poor response to treatment of the depression is associated with increased risk (Modrego & Ferrández, 2004). Understanding the etiology of neuropsychiatric symptoms in MCI may be relevant to understanding the development of dementia (Crocco & Loewenstein, 2005). Future research in mNCD with comorbid NPS should examine conversation rates as well as treatment strategies to reduce progression to major NCD.

Neuropsychiatric symptoms in MCI increase risk for dementia

Neuropsychiatric symptoms in MCI are associated with an increased risk of conversion from MCI to dementia (Rosenberg et al., 2013). Additionally, apart from the difficulties associated with MCI, neuropsychiatric symptoms have serious adverse consequences to the individual, his or her family, and caregivers.

Rosenberg et al. (2013) found baseline neuropsychiatric symptoms in MCI were associated with an increased risk of incident dementia (hazard ratio (HR): 1.37, 95% confidence interval (CI): 1.12−1.66) and AD (HR: 1.35, 95% CI: 1.09−1.66). They concluded that NPS may be among the earliest symptoms of preclinical AD. Palmer et al. (2010) suggested that it is apathy, but not depression that increases risk of progression in aMCI. In another study (Zahodne & Tremont, 2013), apathy and depression were associated with different aspects of executive functioning in aMCI, which may reflect differing patterns of frontal lobe pathology.

Mechanisms reviewed above that underlie the association between depression and risk for cognitive decline are also likely to underlie the association of depression in MCI to the increased risk of dementia (e.g., vascular disease, alterations in glucocorticoid steroid levels, hippocampal atrophy, increased deposition of amyloid-β plaques, inflammatory changes, and deficits of nerve growth factors) (Byers & Yaffe, 2011; Miller, Maletic, & Raison, 2009; Rosenberg et al., 2013). Mood symptoms in MCI may also be related to decreased monoaminergic innervation and neurotransmission (Heneka & O'Banion, 2007; Rosenberg et al., 2013). Researchers have also found that specific neurological changes (e.g., temporal lobe degeneration) associated with MCI and AD are linked to emotional regulation (Sturm et al., 2013).

Anxiety in MCI has also been found to be predictive of dementia (Burton, Campbell, Jordan, Strauss, & Mallen, 2013). Burton and colleagues found the presence of anxiety in MCI to almost double the risk for subsequent dementia. In another longitudinal study of anxiety in MCI (Palmer et al., 2007), 83.3% developed AD vs. 40.9% persons who had MCI without anxiety. However, in one study of patients referred to a memory clinic, anxiety was not associated with increased risk (Ramakers et al., 2010).

Speculation on the causal mechanisms underlying the association of anxiety to dementia includes the possibility that prodromal symptoms of dementia may have caused anxiety. Second, it may be the case that some neurological event may affect the brain in such a manner as to increase anxiety symptoms as well as progression of cognitive decline. Gallacher et al. (2009) suggested the effects may be also indirect. That is, anxiety may affect lifestyle, which in turn has biologic effects. However, it is also the case that anxiety is associated with heightened glucocorticoids, similar to depression, leading to atrophy of the hippocampus. The mechanisms underlying this association are a very important area of future research. Identifying these different etiological factors may have consequences to treatment (Forsell, Palmer, & Fratiglioni, 2003). The neuropsychiatric symptoms are paramount to the clinician treating individuals with cognitive impairment. Nevertheless, in diagnosing NCD using DSM-5, the clinician must be careful not to focus exclusively upon the cognitive impairment and neglect that the primary diagnosis may be major depression or perhaps a psychosis.

Treatment of MCI

First, it must be recognized that at this time, there are no clear treatments for MCI (Cooper, Li, Lyketsos, & Livingston, 2013). There is some evidence supporting the potential role for noradrenergic-based therapies to slow or prevent progressive neurodegeneration in MCI and AD (Chalermpalanupap et al., 2013). In a recent review, polyphenolic compounds (e.g., Ginkgo biloba, green tea, certain fruits, vegetables, wines, Magnolia extract, etc.) were found to exhibit antioxidant and anti-inflammatory activities that may reduce neurodegeneration (Choi, Lee, Hong, & Lee, 2012). In large randomized controlled trials (RCTs), none of these have yet proven effective.

Petersen and Morris (2005) discuss potential options for the treatment of MCI if indeed it is very clear that the

MCI is representative of the prodromal phase of AD. Researchers have suggested that when MCI is likely a prodromal syndrome of AD, clinical trials with disease-modifying drugs that target underlying pathological mechanisms such as amyloid-beta accumulation and neurofibrillary tangle formation may help develop effective treatment options in the future (Karakaya, Fußer, Schroder, & Pantel, 2013). In a recent systematic review (Tricco et al., 2013), cognitive enhancers (e.g., cholinesterase inhibitors and memantine) did not improve cognition or function among patients with MCI and were associated with a greater risk of gastrointestinal harm. Based on this meta-analysis, Russ (2014) concluded that cholinesterase inhibitors should not be prescribed for MCI. In the management of patients with MCI, there should be consideration of addressing vascular risk factors (e.g., hypertension) and other medical issues.

There are also non-pharmacological treatments for MCI. Animal paradigms suggest that exercise may reduce the progression of neurodegenerative disorders such as AD (Hosseini, Alaei, Reisi, & Radahmadi, 2013). Exercise can positively impact cognitive functioning in individuals with MCI (Nagamatsu et al., 2013). Meta-analysis of RCTs documented better cognitive scores after 6–12 months of exercise compared with sedentary controls among patients with dementia or MCI (Ahlskog, Geda, Graff-Radford, & Petersen, 2011). Moreover, one year of aerobic exercise in a large RCT of seniors was associated with significantly larger hippocampal volumes and better spatial memory; other RCTs in seniors documented attenuation of age-related gray matter volume loss with aerobic exercise (Ahlskog et al., 2011). However, others have questioned the magnitude and generalization, and persistence of the effects of exercise on cognition (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013).

Cognitive stimulation has also been used as a treatment for MCI as well as dementia. For example, in a study of cognitive stimulation (Mahjong) and physical exercise (tai chi (TC)) on cognitive performance in persons with dementia, Mahjong and TC were found to preserve functioning or delay decline in certain cognitive domains, even in individuals with significant cognitive impairment (Cheng et al., 2014). Some research has explored the effectiveness of computerized cognitive training in older adults with MCI (Finn & McDonald, 2011). In a recent meta-analysis of cognitive training for healthy older adults and those with MCI, the researchers concluded that such training was effective in improving aspects of objective cognitive functioning; however, whether the effects generalize to improvement in everyday life activities is still unresolved (Reijnders, van Heugten, & van Boxtel, 2013).

Diet may influence risk for dementia. Specifically, diets that promote healthier vascular functioning may decrease risk for NCDs. Frequent consumption of fruits, vegetables, fish, and omega-3-rich oils may decrease the risk of NCD (Barberger-Gateau et al., 2007). Adherence to a Mediterranean diet may contribute to the prevention of a series of brain diseases (Psaltopoulou et al., 2013). In a recent cross-sectional study, high caloric intake was associated with MCI but not moderate caloric intake. However, the authors noted this association is not necessarily a cause−effect relationship (Geda et al., 2013).

Treating neuropsychiatric symptoms in MCI: pharmacological interventions

Pharmacological therapies are not particularly effective for management of neuropsychiatric symptoms of dementia (Sink, Holden, & Yaffe, 2005). There has been little research on the effects of pharmacological treatment of the NPS in MCI. The benefits of treating NPS in MCI are not clear. There are several key questions. Will addressing the NPS in individuals with MCI increase quality of life? Does treatment of the NPS delay progression of cognitive impairment?

Crocco and Loewenstein (2005) concluded that in patients with MCI, it would seem prudent to treat the psychiatric symptoms that are distressing to patients and to avoid medication with anticholinergic side effects. A recent small study found Ginkgo biloba improved NPS and cognitive performance in patients with MCI. The drug was safe and well tolerated (Gavrilova et al., 2014). However, in a large sample, compared with placebo, the use of Ginkgo biloba, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with MCI (DeKosky et al., 2008).

Most of what we know in this area, however, comes from research in the treatment of NPS in dementia – but not MCI. There has been some research examining the treatment of depression in patients with dementia. Results have been mixed with researchers noting that lack of power in studies may have led to limited effects (Nelson & Devanand, 2011). There is some indication that treatment with a selective serotonin reuptake inhibitor (SSRI) may improve cognitive function and daily living (Kessing, Søndergård, Forman, & Andersen, 2009); whereas the anticholinergic effects of the tricyclics may worsen cognition. Additionally, there have been negative findings reported, suggesting that antidepressant may not confer benefit (Enache, Winblad, & Aarsland, 2011).

Recently, Rosenberg et al. (2012) reviewed the literature regarding possible benefits and disadvantages of using psychotropic medications (e.g., antidepressants and antipsychotics) for individuals with NPS in dementia. They note that despite their wide use, benefits have not been established; indeed, there is evidence that such psychotropic medications may be associated with worse cognitive outcomes. Rosenberg et al. (2012) conducted a longitudinal, observational study examining the association of psychotropic medication use with cognitive, functional, and neuropsychiatric symptom trajectories among community-ascertained incident AD cases from the Cache County Dementia Progression Study. A total of 230 participants were followed for a mean of 3.7 years. They found that psychotropic medication use was associated with more rapid cognitive and functional decline in AD, and not with improved NPS. However, this was an observational study and the researchers note that clinicians may have prescribed psychotropic medications to AD patients

who were perceived to be at greater risk of poorer outcomes. Nonetheless, findings are consistent with the possibility that poorer outcomes were caused by psychotropic medications.

Importantly, research in this area was conducted on individuals with dementia. The question remains – are there potential beneficial effects associated with the use of neuropsychiatric medications in individuals with mNCD with behavioral symptoms? Can such treatment reduce the NPS? Can treatment slow progression of cognitive impairment? Can treatment improve quality of life? Further, do treatment outcomes vary with the likely etiologies associated with the mNCD?

It may be the case that treatment of depression and other NPS in dementia may not be beneficial. However, we do not know if treatment of depression in mNCD may have a different and more positive trajectory. Leonard (2007) suggested that the efficacy of antidepressant treatments appears to depend on the phase of development of depression. Once neuronal damage has reached a stage at which the functional integrity of specific brain regions cannot be reversed, antidepressant treatment may be ineffective (Leonard, 2007).

Psychosocial treatments of neuropsychiatric symptoms in MCI

Psychosocial interventions for patients with mNCD with neuropsychiatric features may be beneficial; however, most studies have examined the efficacy of treating neuropsychiatric symptoms in dementia – but not in MCI. In a landmark, clinical investigation of two non-pharmacological treatments of depression in patients with AD, one emphasizing patient pleasant events and one emphasizing caregiver problem solving, indicated that the behavioral interventions are important and effective strategies for treating depressive symptoms in demented patients (Teri, Logsdon, Uomoto, & McCurry, 1997).

In a recent meta-analysis (Orgeta, Qazi, Spector, & Orrell, 2014), researchers attempted to examine the effectiveness of psychological-behavioral treatment for individuals with NPS in dementia. The types of psychological intervention varied (e.g., therapeutic counseling, counseling with education and support, cognitive behavioral therapy (CBT), TC exercises, and interpersonal psychodynamic therapy). Results pooled from the six RCTs showed that psychological treatments reduced depressive and anxiety symptoms in people with dementia. However, they found no effect of these psychological treatments on any of the secondary outcomes (e.g., activities of daily living, quality of life, and other neuropsychiatric symptoms or cognition). In additional studies in patients with depression and dementia, problem-solving therapy and CBT were found to be useful in decreasing depressive symptoms and disability (Alexopoulos, Raue, & Arean, 2003; Kasl-Godley & Gatz, 2000). Behavioral activation approaches tailored to the interests and capabilities of the individual may also be effective (Potter & Steffens, 2007).

In future research, we need to better understand the interplay between emerging symptoms of cognitive impairment and the development of neuropsychiatric disorders. Specifically, what is the etiology of NPS in mNCD? Are the NPS a manifestation of neurological cognitive problems? Does some neurological event affect both cognition and NPS? Or in some cases, does the neuropsychiatric disorder result from the distress caused by growing cognitive impairment? Identifying these different etiological factors may have consequences to treatment of both the NPS and the cognitive impairment (Forsell et al., 2003). Can direct treatment of the neuropsychiatric disorder improve quality of life and help reduce the progression of cognitive decline (Armstrong, Midanik, & Klatsky, 1998)? A better understanding of the psychiatric features in mNCD may ultimately lead to a better understanding of etiology as well as treatment strategies.

Summary

A pivotal addition to the DSM-5 is the diagnosis of 'mNCD'. The diagnosis of mNCD is defined by a noticeable decrement in cognitive functioning that goes beyond normal changes seen in aging. Presently, our understanding of mNCD is derived in large part from research in MCI. With the specific criteria as now defined by the DSM-5 for mNCD, many experimental therapies now and into the future will focus on decreasing the risk of progression from mNCD to major MCI. Second, researchers have found the presence of neuropsychiatric symptoms (NPS) is quite common among individuals with MCI and is an important risk for progression to dementia. It is imperative that future research examines effective treatments for NPS in mNCD. Clinicians and clinical investigators must determine if treatment of neuropsychiatric disorders in mNCD will improve quality of life and reduce the progression of the disorder.

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