Commentary on Phosphodiesterase 5 Inhibitor Mirodenafil Ameliorates Alzheimer-Like Pathology and Symptoms by Multimodal Actions

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COMMENT:

In 2018 a research framework was published [1] outlining a biologic definition of Alzheimer's disease. In that paper it was stated that Alzheimer's disease "refers to Aβ plaques and pathologic tau deposits, defined *in vivo* by abnormal biomarkers of Aβ and pathologic tau (both are required)". This was done to further define Alzheimer's disease which had been previously defined [2] as a clinical-pathologic entity diagnosed definitely at autopsy and in life as possible or probable AD. But the 2018 research framework authors themselves admitted that what they produced was a "unifying update for use in observational and interventional research, not clinical care." In clinical care it is not always possible to get biomarkers due to cost, lack of insurance coverage and availability. This limits clinicians in making a definitive diagnosis of AD and forces a clinician to use the 2011 definition of "possible or probable AD" or the 2018 definition "Alzheimer's Clinical Syndrome" for patients without a known biomarker — which does not exclude patients with mixed dementia due to cerebrovascular disease or those with Parkinsonism or Dementia with Lewy Bodies to name simply a few of the many clinical syndromes that can clinically masquerade as AD. And since the etiology of dementia is multifactorial it can not be extrapolated that a benefit in Alzheimer's disease (as defined by two specific biomarkers) would help the great majority of people with dementia in this country who do not have a defined biomarker.

It is then as a clinician that I write this commentary and applaud Byung Woo Kang, et al for expanding on the 2018 framework that stated "Although it is possible that β-amyloid plaques and neurofibrillary tau deposits are not causal in AD pathogenesis, it is these abnormal protein deposits that define AD as a unique neurodegenerative disease". There is no doubt that to find a specific treatment for Alzheimer's disease we need to consistently define what AD is as an entity. But the opposite is not true — a treatment for AD does not necessarily need to only treat the pathology that exists in the definition alone. In fact, since "there isn't a single cause of Alzheimer's disease" [3] we should hope that a drug — or set of drugs — can treat all facets that lead to Alzheimer's disease and dementia. This includes reducing Aβ and phosphorylated tau burden but also improving neurotransmission, decreasing oxidative stress, increasing cerebral blood flow (CBF), protecting the mitochondrial membrane and reducing neuroinflammation — all noted benefits of mirodenafil as noted in this paper.

In conclusion Alzheimer's disease is a complex disease and dementia is multifactorial in its etiology and if we do not treat all facets we are not treating the whole person.

REFERENCES

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