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Commentary Open Access

Commentary: A retrospective classification of diagnoses in terms of DSM-5 for patients included in randomized controlled trials of Ginkgo biloba extract EGb 761®

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When the first clinical trials of *Ginkgo biloba* extract in aging-associated cognitive disturbances were conducted, such disturbances were widely considered to be related to compromised cerebral perfusion. Enhancement of peripheral and cerebral perfusion had been reported earlier from pre-clinical and clinical trials with *Ginkgo biloba* extract EGb 761®, rendering this phytomedical drug a candidate for the treatment of aging-associated cognitive disorders[1,2]. However, stringent and generally accepted diagnostic criteria to identify and characterise patients for clinical research were not available at that time. Hence, patients for clinical trials were selected in a pragmatic manner and a variety of unspecific designations, such as *cerebro-vascular insufficiency*, *organic brain syndrome* or *disturbance of cerebral function*, rather than precisely defined diagnostic terms, were used for the conditions that needed to be treated. Whether such studies enrolled patients with mild cognitive impairment (MCI), full-blown dementia or both was determined by the selection criteria rather than by any diagnostic terms.

When assessing the overall evidence of efficacy and safety of EGb 761® for a disorder now defined according to modern diagnostic criteria, it is inappropriate to run meta-analyses across all of the randomized controlled trials (RCTs) available, without taking into account the inclusion diagnoses and diagnostic criteria applied, as an earlier Cochrane review did[3]. The question that evidence-based medicine is supposed to answer is whether a treatment is likely to benefit a patient with an identifiable disorder or condition[4]. A prerequisite for meaningful aggregation and meta-analysis of data from different clinical trials is therefore that the diagnosis is known for all patients at a reasonable level of accuracy, in order for the results to be interpreted with respect to the condition of a patient seeking help. As the 5th revision of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5)[5] provides criteria for the pre-dementia (MCI) and dementia stages of vascular and primary degenerative (Alzheimer's disease, AD) neurocognitive disorders within one diagnostic system, we aimed to retrospectively classify the patient samples in RCTs of EGb 761® in terms of DSM-5 diagnostic categories.

Randomized, controlled, double-blind trials of EGb 761® in cognitive ailments and disorders were identified by an extensive literature search and an inquiry to the manufacturer about unpublished trials in the context of the 2011 call for scientific data on *Ginkgo biloba* by the Committee of Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA). When we embarked on the retrospective classification, the data from all relevant trials (31 RCTs) had already

been published. All pertinent information provided in the published papers (e.g. inclusion and exclusion criteria, baseline characteristics) was used to check if the criteria for a neurocognitive disorder (NCD) were met and, if so, whether it was mild or major NCD. In a second step, we attempted to distinguish between AD and vascular aetiology. If the published information was not sufficient to enable classification by disorder, stage and aetiology, the study reports were retrieved, as far as accessible.

Due to the high concordance between the respective criteria, patients diagnosed with dementia in accordance with earlier DSM editions, the 10th edition of the International Classification of Diseases (ICD-10)[6], the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[7] or the National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neursciences (NINDS-AIREN)[8] could easily be classified under major NCD and sub-classified by probable aetiology (AD, vascular, mixed). Nine RCTs enrolled patients with major NCD. Of these, four admitted patients with NCD due to probable AD, probable vascular NCD or NCD due to multiple aetiologies (AD and vascular pathology); two admitted patients with NCD due to probable AD or probable vascular NCD, but not mixed forms; and three only admitted patients with NCD due to probable AD.

Various concepts for cognitive impairment in the elderly not meeting criteria for dementia were developed during the 1990s; international consensus diagnostic criteria for MCI were published only in 2004[9]. Checking the eligibility criteria and patient characteristics in studies of non-demented patients against the DSM-5 criteria for mild NCD was therefore less straightforward and in some instances required information from study reports. Nevertheless, patients from ten RCTs could be classified under mild NCD. Most trials in mild NCD did not distinguish diagnoses by aetiology; two trials selected patients with possible vascular pathology and one trial enrolled patients with supposed AD pathology. Four of these trials permitted an unambiguous diagnosis of mild NCD in all patients. In six trials it could not be verified for all patients with sufficient certainty that the cognitive deficits did not interfere with independence of everyday activities. It is therefore possible that a small proportion of patients enrolled in these trials might already have been in the mild stage of major NCD. Taking into account that the key criterion for the distinction between mild and major NCD (or between MCI and dementia), i.e. interference with independence in everyday activities (or interference with social or occupational functioning) has never been operationalized sufficiently well to strictly and unambiguously distinguish between the two conditions, and that the disease is actually the same before and after crossing this fuzzy line, the inclusion of patients with mild NCD along with those in the mild stage of major NCD into the same study is nowadays considered acceptable[10,11].

Finally, there were eight RCTs for which a classification by DSM-5 was not possible. For some of these trials, the available information was not sufficient to verify any of the diagnoses in question; other studies used selection criteria that did not strictly exclude patients with mild NCD, but also admitted those with cognitive performance adequate for age (i.e. aging-associated memory impairment).

Retrospectively classifying patients enrolled in clinical trials that were conducted during the last 30 years may appear to be quite an academic undertaking with little bearing on today's treatment decisions. This would, however, be an imprudent conclusion. Elderly doctors probably have a notion of what a patient with *cerebro-vascular insufficiency* or *disturbance of cerebral function* (in German: *Hirnleistungsstörung*) is like, which diagnostic and therapeutic measures are appropriate, and what modern diagnosis may apply. But how can young doctors or students understand and interpret the papers reporting older studies? With the classification in terms of DSM-5, young scientists and physicians who are used to modern diagnostic terms can understand which disorders the patients enrolled in these studies were actually suffering from. It may be argued that inclusion criteria phrased many years ago against a different background and experience might be interpreted somewhat differently today. This is possible, indeed, but the same would apply to formal diagnostic criteria as well. Even at one point in time, the understanding and interpretation of formal criteria may vary to some extent across different regions, cultural backgrounds and languages. Apart from such slight inherent "fuzziness", a good understanding of inclusion diagnoses helps today's physicians and scientists to interpret older clinical trials and to appreciate the evidence of efficacy and safety resulting from both earlier and later trials with regard to the patients they encounter.

Conflict of Interest

RH is a full-time employee of Dr. Willmar Schwabe GmbH & Co. KG, receiving a fixed salary.

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