

NEUROPSYCHIATRIC OUTCOME FOR CLINICAL TRIALS

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Neuropsychiatric symptoms, also referred to as 'BPSD' (Behavioural and Psychological Symptoms of Dementia) or 'challenging behaviour', are now proposed as a major component of the dementia syndrome and are as clinically significant as disorders of cognition. There is a growing interest in these symptoms as they are present since the early stage of the disease, constitute a marker of disease progression, are responsible for a large share of the suffering of patients and caregivers, and strongly determine the patient's lifestyle and management.

Behavioural changes are not only important at a symptomatic level but could be a key feature

for the future disease modifying therapies. The final aim of such therapies is to modify the long term outcome of the patients and to delay the progression to the most severe stage of the disease. As neuropsychiatric symptoms become on average more frequent with the disease progression their assessment in the course of a trial is particularly relevant on the effect of disease-modifying agents. In this context it is important to improve the quality of the available clinical instruments.

Clinical trial instrumentation

In clinical trials neuropsychiatric symptoms have most commonly been assessed via the Neuropsychiatric Inventory (NPI). The NPI, using a caregiver interview, with rating of the frequency and severity of 10 or 12 neuropsychiatric domains (according to the version).

A moderate but significant effect was found for antedementia agents that are currently available (1). When used as a secondary outcome the NPI has shown short term-term behavioural improvement or stabilisation in clinical trials (2).

Most of the studies used the total NPI score representing the sum of the 12 neuropsychiatric frequency x severity score. This is inappropriate because adding up various symptoms with different etiologies is without real clinical significance. In addition results also indicated high standard deviations of measurement within trials reflecting important variability.

NPI sub syndromes scores in clinical trials

It is therefore recommended to assess differences between scores for a subgroup of behavioural domain. In fact a large amount of data support the notion that 'behavioural disorders' is an umbrella concept and should rather be considered as groups of subsyndromes, each reflecting a different prevalence,

course over time, biological correlates and psychosocial determinants. Furthermore, the identification of sub-syndromes may point to a common neurobiological pathogenesis, or may react to the same treatment. In order to identify neuropsychiatric sub-syndromes of the NPI, several factor analysis has been done. Recently, cross-sectional data of 2354 patients with AD from 12 centers from the European Alzheimer's Disease Consortium (EADC) were collected. Principal component analysis was used for factor analysis (3). Results showed the presence of four consistent neuropsychiatric sub-syndromes, named hyperactivity, psychosis, affective and apathy (table 1). These four subsyndromes have been used in order to characterize the neuropsychiatric symptoms in the EADC study ICTUS (Impact of Cholinergic Treatment Use). Results indicated that more of 65% of the patients present at least one of the NPI syndromes (figure 1 & 2).

NPI frequency x severity scores in clinical trials

In order to have a clinically relevant assessment the other option is to use the single NPI items

(score reflecting the change in one behavioural domain, or symptoms emergence). This has already been done in the past in various drug trials. This approach however raises another problem related to the nature of the score. For each domain both the severity and frequency of each symptom is scored on the basis of structured questions administered to the patient's informant. The final score for each item is obtained by multiplying severity (1-3) by frequency (1-4). Although this approach has been cross-validated in several studies, a disadvantage is its non-linear aspect in higher range of the scale, because as a result of this multiplication an item-score of 5, 7, 10 and 11 doesn't exist. Furthermore this score also raise the same difficulty as the total score (sum of the different behavioural domains) because merging different types of information and by the way leading to an evaluation not totally close to the clinical practice. These considerations suggest that it may be more relevant to separately rate frequency and severity. Frequency score is particularly interesting in clinical practice For example for the majority of the symptom domains reducing the score from "present everyday" to "present only one or several time in the week" is a meaningful result both for the patient and the caregiver.

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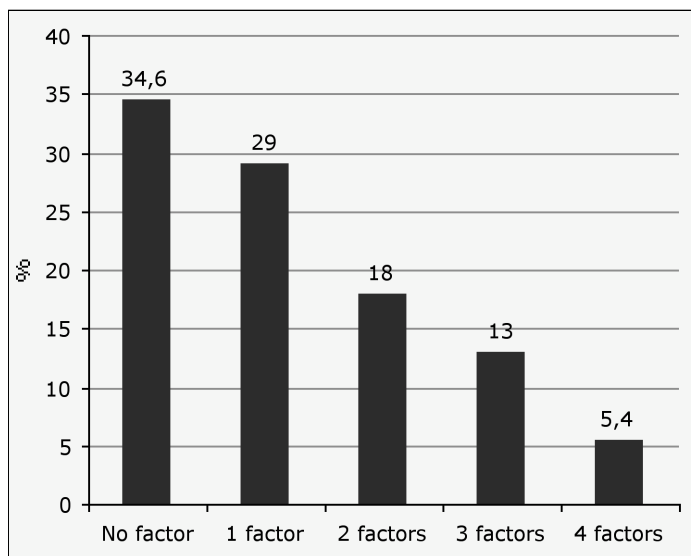
Table 1
EADC factor analysis of the NPI

	Factor 1: hyperactivity	Factor 2: psychosis	Factor 3: affective	Factor 4: apathy
Delusions	0.294	0.707	0.063	-0.018
Hallucinations	0.134	0.808	0.054	-0.011
Agitation	0.700*	0.112	0.274	0.036
Depression	0.069	0.052	0.728	0.206
Anxiety	0.154	0.141	0.706	0.023
Euphoria	(0.359)**	0.049	-0.355	0.207
Apathy	0.121	-0.141	0.184	0.629
Disinhibition	0.682	0.139	-0.119	0.030
Irritability	0.707	0.093	0.278	0.026
Aberrant motor behaviour	0.432	0.222	-0.118	(0.412)
Night time behaviour disturbances	-0.054	0.510	0.157	(0.431)
Appetite and eating abnormalities	0.000	0.105	-0.011	0.705
Eigenvalues	2.772	1.264	1.117	1.063
Variance, %	23.10	10.54	9.31	8.86

* bold font indicates factor loading equal or greater than 0.40; ** parenthesis indicates factor loading just below criteria equal or greater than 0.40

Figure 1

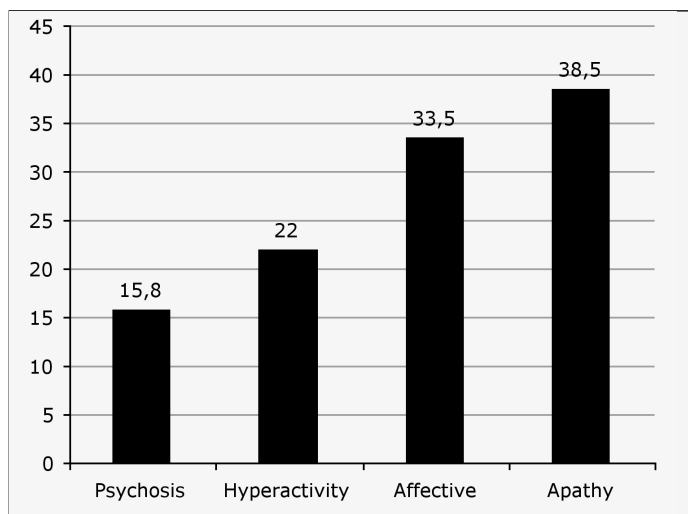
Frequency (%) of the 4 NPI sub syndromes in the ICTUS EADC study



ICTUS is a prospective longitudinal study done within the network of EADC. 29 centers in 12 different European countries participated and recruited 1350 AD patients. To be considered as clinically relevant, the score of each symptom must be greater than 3. Mean age of the patients at baseline was 76.24 ± 7.71 years, 570 (42.22%) reported a CDR score of 0.5, 599 (44.37%) a score of 1, 169 (12.52%) a score of 2 and 12 (0.89%) a score of 3.

Figure 2

Cumulative frequency (%) of each NPI sub syndromes in the ICTUS EADC study



Specific behavioural evaluation

Other scales have been proposed to assess a particular type of challenging behaviour in more depth. Examples of these scales are the Cohen-Mansfield Agitation Inventory (4), the Cornell Scale for Depression in Dementia (5) or the Apathy Inventory (6). These instruments have all been validated in several settings, and translations are available in most of the western languages. The apathy and depression instruments are particularly important in the early, mild stage of the disease.

Combined measures

An effective approach to measure neuropsychiatric symptoms is to combine a general scale such as the NPI with more detailed scales that focus on specific types of behaviour, especially those that may be closely linked to the Alzheimer substrate. Taking into account that the caregiver point of view have some limitations, it is also needed to promote the development of scales combining caregiver, patient and clinician point of view. The latter one have to be based on the observation of the patient during the medical - neuropsychological visit.

Key points

Given the substantial increase of knowledge on neuropsychiatric aspects of dementia over the past years and the importance of the problem in clinical practice, the time is now ripe to include more specific measures for particular types of problem behaviour in future drug trials (7). The following points are suggested:

- to avoid the use of BNPI total score
- to use NPI sub syndrome or single item score

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- to separate the frequency and severity assessment
- to use in combination with the NPI specific behavioural domains scale
- to promote the combination of caregiver, clinician and patient point of view

References

1. Cummings JL, Zhong C. Treatment for behavioural disorders in neurodegenerative diseases: drug development strategies. *Nature reviews Drug Discovery* 2006;5:64-74.
2. Geldmacher D, Frolich L, Doody RS, Erkinjuntti T, Vellas B, Jones RW, et al. Realistic expectations from treatment success in Alzheimer's disease. *The Journal of Nutrition Health and Aging* 2006.
3. Aalten P, Verhey F, Boziki M, Bullock R, Byrne EJ, Camus V, et al. Neuropsychiatric syndromes in dementia; results from the European Alzheimer Disease Consortium. *Dement Geriatr Cogn Dis* in press.
4. Cohen-mansfield J. Agitation in the elderly. *Advances in psychosomatic medicine: Geriatric psychiatry*. In: Bilig N, Rabins P, editors. 0 ed. Switzerland: Karger,S.; 1989. p. 101-113.
5. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biological Psychiatry* 1988;23:271-284.
6. Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, et al. The Apathy Inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *International Journal of Geriatric Psychiatry* 2002;17:1099-1105.
7. F. Cortes et al, Six and 18-month Changes in Mild to Moderate Alzheimer's Patients Treated with Acetylcholinesterase Inhibitors: What Can we Learn for Clinical Outcomes of Therapeutic trials? *J Nutr Health Aging* 2007, 11, 4: 330-337.