

TOP CITED PAPERS IN *INTERNATIONAL PSYCHOGERIATRICS*: 6b. BEHAVIORAL DISORDERS AND CAREGIVERS' REACTION IN TAIWANESE PATIENTS WITH ALZHEIMER'S DISEASE

Reflection

The behavioral and psychological symptoms of dementia (BPSD) are common and serious problems that affect the quality of life of the patients who experience such symptoms as well as their caregivers (Matsui *et al.*, 2006). BPSD present a major challenge in the medical management of cognitively impaired patients. Our paper entitled "Behavioral disorders and caregivers' reaction in Taiwanese patients with Alzheimer's disease" (hereafter referred to as the "paper") (Fuh *et al.*, 2001) has been cited widely, reflecting the importance of these clinical issues and the growing international interest in studies of BPSD.

A valid and reliable evaluating instrument is essential to detect and study BPSD. The aims of the paper were to evaluate the applicability of the Chinese (Taiwanese) version of the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994), and to explore the neuropsychiatric manifestations of Taiwanese patients with Alzheimer's disease (AD) and the associated caregiver distress (Fuh *et al.*, 2001). The NPI was developed to assess psychopathology in dementia patients and is one of the most commonly used instruments to evaluate BPSD. It evaluates 10 neuropsychiatric disturbances often observed in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition and aberrant motor behavior. The night-time behavior disturbances and appetite and eating abnormalities were added to the NPI later (NPI-12) (Cummings, 1997). A nursing home version also was developed for use by professional caregivers within institutions (Wood *et al.*, 2000). The severity and frequency of each neuropsychiatric symptom are rated on the basis of scripted questions administered to the patient's caregiver. The NPI also assesses caregiver distress engendered by each of the neuropsychiatric disorders. The NPI provides a clear and simple description of each symptom and assists researchers and clinicians to better define each symptom of BPSD. The high cross-cultural reliability of the NPI is based on its highly structured format and scripted questions.

We have reviewed the 32 articles that cited our paper and discovered that 18 of them (56.2%) found the paper of interest because it provided evidence

of the existence of neuropsychiatric sub-syndromes in dementia. Six articles (18.9%) cited the paper because of cross-cultural comparisons of BPSD, a growing area of interest in dementia and BPSD research.

BPSD refers to a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors occurring in people with dementia. Factor analysis techniques have been used to explore behavioral dimensions that may comprise BPSD. Table 1 summarizes studies using factor analytic techniques to identify the subsyndromes contained within the NPI (Frisoni *et al.*, 1999; Fuh *et al.*, 2001; Aalten *et al.*, 2003; Lange *et al.*, 2004; Mirakhur *et al.*, 2004; Borroni *et al.*, 2006; Hollingworth *et al.*, 2006; Matsui *et al.*, 2006; Aalten *et al.*, 2007; Zuidema *et al.*, 2007). Three to five sub-syndromes were found in these studies and different terms were used to label them. Despite some differences among these studies, the associations of the following symptoms were very consistent: (1) depression and anxiety, (2) delusions and symptoms of hallucination, (3) agitation and irritability, (4) disinhibition and euphoria. The symptoms were in the same sub-syndrome in most of the reviewed studies and across various cultural settings, suggesting that these four common sub-syndromes may reflect four distinctive pathophysiological disorders (Robert *et al.*, 2005). More studies are needed to determine if these four sub-syndromes also share treatment-related characteristics.

Apathy and aberrant motor activities are two symptoms that had variable associations with other individual symptoms in different patient populations. Apathy was associated with depression in some studies (Aalten *et al.*, 2003; 2007; Hollingworth *et al.*, 2006), with aberrant motor activities in others (Frisoni *et al.*, 1999; Lange *et al.*, 2004; Mirakhur *et al.*, 2004; Matsui *et al.*, 2006; Zuidema *et al.*, 2007), or with other symptoms in some studies (Fuh *et al.*, 2001; Borroni *et al.*, 2006; Zuidema *et al.*, 2007). The relationship between depression and apathy is controversial. It is recognized that apathy overlaps with depression, which is not surprising considering that common symptoms of both syndromes include diminished motivation and interest as well as lack of insight. The major difference is that apathy may occur in the absence of depressed mood. One study showed that

Table 1. Results of previous factor analytic studies using the NPI

AUTHORS	YEAR	COUNTRY	NUMBER OF PATIENTS	MEAN MMSE SCORE	NPI VERSION	FACTORS
Frisoni <i>et al.</i>	1999	Italy	162	13.3	NPI-10	Mood/frontal/psychosis
Fuh <i>et al.</i>	2001	Taiwan	95	12.7	NPI-10	Mood-psychosis/psychomotor regulation/social engagement
Aalten <i>et al.</i>	2003	Netherlands	199	18.1	NPI-12	Mood-apathy/psychosis/hyperactivity
Lange <i>et al.</i>	2004	Canada	204		NPI-NH	Agitation/mood/psychosis/sleep-motor activity/elevated behavior
Mirakhor <i>et al.</i>	2004	Northern Ireland	435	13	NPI-12	Affect/physical behavior/psychosis/hypomania
Borromi <i>et al.</i>	2006	Italy	232	17.7	NPI-12	Psychosis/moods/apathy/frontal
Hollingworth <i>et al.</i>	2006	U.K.	1120	12.8	NPI-12	behavioral dyscontrol/psychosis/mood/agitation
Matsui <i>et al.</i>	2006	Japan	140	20.3	NPI-10	Psychosis/mood/euphoria
Aalten <i>et al.</i>	2007	12 European countries	2354	17.8	NPI-12	Hyperactivity/psychosis/affective symptoms/apathy
Zuidema <i>et al.</i>	2007	Netherlands	1437		NPI-NH	Agitation-aggression/depression/psychosis/psychomotor agitation/apathy

the associations of apathy with depression changed as the disease progressed (Hollingworth *et al.*, 2006), possibly explaining some conflicting study results. Studies using positron emission tomography (PET) and single emission computed tomography (SPECT) to establish regional cerebral metabolism or perfusion showed that regions of dysfunction associated with these two syndromes were different. Patients with apathy showed involvement of the anterior cingulate and related frontal-subcortical circuit structures (Craig *et al.*, 1996; Benoit *et al.*, 1999), patients with depression evidenced more abnormalities of frontal, temporal and parietal areas (Starkstein *et al.*, 1995; Hirono *et al.*, 1998).

Aberrant motor activities had no consistent associations with any individual symptoms. Aberrant motor activities comprise symptoms like pacing, constant opening/closing wardrobes, repeatedly dressing or undressing and picking/fiddling or other repetitive behavior (Cummings *et al.*, 1994). This syndrome is least well understood of all those identified by the NPI and warrants further study.

BPSD no doubt stem from a complex interaction among biological, environmental and cultural factors (Fuh *et al.*, 2002). Similar behavioral sub-syndromes identified across different cultures suggests that the observed behaviors are more related to a common underlying biological dysfunction whereas differing patterns of behavior may indicate that cultural or environmental influences may be more relevant. Our previous transcultural study (Fuh *et al.*, 2002) of three countries – Taiwan, Italy and the U.S.A. – showed a significant relationship between agitation and hallucinations in the Taiwanese group and a significant relationship between agitation and apathy in the Italian group. In the American group, agitation and irritability were associated. We found different behavioral profiles accompanying agitation in the three cultural groups. This study highlighted the importance of cultural factors in some symptoms of BPSD.

Many transcultural questions pertaining to dementia remain unanswered, and there is a relative paucity of research on dementia in non-Western societies. The conduct of cross-cultural studies using standardized sampling, diagnostic and assessment methods could contribute to our understanding of the interplay between genetic and environmental risk factors. Including our Chinese version, the NPI has been translated into a variety of languages with proven validity and reliability (Hirono *et al.*, 1997; Binetti *et al.*, 1998; Choi *et al.*, 2000; Fuh *et al.*, 2001; Leung *et al.*, 2001; Baiyewu *et al.*, 2003; Lange *et al.*, 2004; Politis *et al.*, 2004; Camozzato *et al.*, 2008; Selbæk *et al.*, 2008), facilitating further transcultural study of BPSD.

This study followed a period during which Dr. Fuh trained with Dr. Cummings at UCLA. Dr. Fuh became familiar with research strategies and approaches involving the NPI and related assessments. Successful implementation of these skills in Taiwan resulted in the study documented in the paper. Such cross-national training is essential to enhance research worldwide.

Many new agents are evolving for the treatment of AD (Salloway *et al.*, 2008). To build sufficient sample size to test these agents, global trials will be required. Cross-cultural studies of instruments such

as those conducted with NPI are critically important to designing and interpreting the data from these trials.

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Commentary

As Fuh and Cummings point out above, it is no coincidence that their paper (Fuh *et al.*, 2001) was equal sixth in the number of citations received by all papers published in *International Psychogeriatrics* to the end of 2006 with 31 citations. This is because BPSD encompass key elements of the dementia syndrome and are prime drivers of major shifts in care and treatment. To underline the initial point, the first patient with Alzheimer's disease ever to be described, Augusta D, had prominent agitated behavior and intermittent delusional ideas (Maurer *et al.*, 2006). To address the second point, very few people with dementia get admitted to residential care because they cannot remember the date, and even fewer are prescribed antipsychotic drugs because they cannot spell "world" backwards. Behaviors whose expression is captured by the NPI, such as sleep disturbance, excess motor activity and resistiveness to care, are common reasons for dedicated family members to acknowledge with reluctance that they can no longer care for the person they love at home and to seek that person's admission to residential care. Delusions, hallucinations, misidentifications and aggressive behavior are frequent indications leading to the prescription of antipsychotic drugs, which have the potential both to help and to harm patients (Suh, 2009) and the NPI is designed to note the presence, intensity and caregiver distress produced by these symptoms. The importance and topicality of this area of research is illustrated by a quick flick through the last three years of this journal's regular issues from December 2006 to October 2009 (18 issues). Of 48 review articles published over this period, ten (20.8%) (Filan and Llewellyn-Jones, 2006; Lyketsos, 2007; Kononov *et al.*, 2008; von Gunten *et al.*, 2008; Beaulieu-Bonneau and Hudon, 2009; Haw *et al.*, 2009; Kverno *et al.*, 2009; O'Connor *et al.*, 2009a; 2009b; Rodda *et al.*, 2009) dealt with some aspect of the BPSD spectrum in

people with cognitive impairment, while 26 of 233 original research articles (11.2%) (Holmes *et al.*, 2006; Lövheim *et al.*, 2006; 2008; 2009a; 2009b; Svansdottir and Snaedal, 2006; Bird *et al.*, 2007; Davison *et al.*, 2007; Kessing *et al.*, 2007; Lanctôt *et al.*, 2007; Liu *et al.*, 2007; Rabinowitz *et al.*, 2007; Cankurtaran *et al.*, 2008; Haw *et al.*, 2008; Nakaaki *et al.*, 2008; Rozzini *et al.*, 2008; Treiber *et al.*, 2008; Borroni *et al.*, 2009; Burns *et al.*, 2009; Eggermont *et al.*, 2009; Kleijer *et al.*, 2009; Nijk *et al.*, 2009; van der Geer *et al.*, 2009; Weamer *et al.*, 2009; Woods *et al.*, 2009; Wu *et al.*, 2009) also focused upon BPSD in dementia and related conditions in some shape or form.

Because dementia is a global challenge of rapidly growing proportions, and one that is growing fastest in the developing world (Ferri *et al.*, 2005), we need translations of instruments which will be useful in populations whose languages are not those of the instruments' original designers, most of whom have developed their tools to be used in the English language. Again, *International Psychogeriatrics* illustrates this point. Since December 2006, 20 original research articles (Hendrie *et al.*, 2006; Awata *et al.*, 2007; Chachamovich *et al.*, 2007; Falk *et al.*, 2007; Malakouti *et al.*, 2007; Nuevo *et al.*, 2007; Tsai *et al.*, 2007; Camozzato *et al.*, 2008; Chaaya *et al.*, 2008; Chu and Chung, 2008; Leung *et al.*, 2008; Selbæk *et al.*, 2008; Skjerve *et al.*, 2008; van der Roest *et al.*, 2008; Dodge *et al.*, 2009; Fernandes *et al.*, 2009; Gibbons *et al.*, 2009; Perrocco *et al.*, 2009; Tiwari *et al.*, 2009; Wong and Fong, 2009), representing 8.6% of all such articles published in the journal that address the translation or validation of rating scales or assessment instruments in languages other than English, have been published within these pages. The International Psychogeriatric Association (IPA) exists partly in order to promote the spread of knowledge and to enable dissemination of best practice in order to benefit everyone in the world in relation to mental

health and illness in late life, no matter where they live. Fuh *et al.* illustrated in their article the importance of this activity, and it is no coincidence that it has been highly cited. Its continued frequent citation is one illustration of the fact that IPA's journal continues to fulfill at least some of the objectives of IPA's founders and their successors

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