Scales to Assess Efficacy and Safety of Pharmacologic Agents in the Treatment of Behavioral and Psychological Symptoms of Dementia

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Advances in the assessment of the behavioral and psychological symptoms of dementia (BPSD) have been employed in large-scale clinical trials of new antipsychotic medications such as risperidone. These scales can be used to assess drug efficacy and to compare different treatment regimens. We review 3 valid and reliable scales, the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Cohen-Mansfield Agitation Inventory (CMAI), and the Neuropsychiatric Inventory (NPI). Extrapyramidal side effects (EPS) associated with the treatment of BPSD have also been assessed using a number of rating instruments. The design of the most comprehensive of these, the Extrapyramidal Symptom Rating Scale (ESRS), is exhaustive, and it successfully quantifies EPS and distinguishes toxic from nontoxic medications. This publication serves as an aid to researchers and clinicians in their interpretation of qualitative and quantitative data from trials evaluating antipsychotic agents in the treatment of BPSD. *(J Clin Psychiatry 2001;62[suppl 21]:19–22)*

Psychosis, aggression, and agitation are among the most problematic symptoms of dementia. The management of agitation and related problems in patients with dementia has been marked by a history of sporadic research and the overuse of psychotropic medications for poorly defined target symptoms. There has, however, been a recent renaissance, marked by advances in the assessment of behavioral symptoms and larger-scale randomized clinical trials of newer antipsychotic medications and other agents.[1] For example, trials have recently been published using the novel antipsychotic medication risperidone for the treatment of behavioral and psychological symptoms of dementia (BPSD).[2,3] Efficacy in the BPSD indication can and should be demonstrated by the use of well-validated and drug-sensitive behavioral scales. In this article, we elaborate on 3 scales suitable for assessing efficacy in clinical trials—the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[4] the Cohen-Mansfield Agitation Inventory (CMAI),[5-7] and the Neuropsychiatric Inventory (NPI).[8,9] It should be noted that the BEHAVE-AD and the NPI have a considerable degree of overlap and measure the same sorts of behaviors in similar types of patients. Two of these scales, the BEHAVE-AD and the CMAI, were used in the clinical trials mentioned above,[2,3] which involved about 1000 individuals suffering from dementia.

With regard to the safety of new medications, a number of rating instruments have been developed to quantify aspects of the extrapyramidal side effects (EPS) associated with the treatment of BPSD. In general, these instruments are designed to capture only 1 or at most 2 of the 3 categories of EPS. A notable exception to this trend is the Extrapyramidal Symptom Rating Scale (ESRS),[10] which is designed to capture virtually all aspects of treatment-emergent EPS. Because of its length and complexity, its use has been confined almost exclusively to clinical research trials. Here we review the design and implementation of the ESRS and provide a number of examples from the literature of controlled trials.

EFFICACY

Clinical interviews with patients and their relatives provide much information on the disease process and the extent of BPSD that the patient is suffering from. This type

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Table 1. Clusters Assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[a]

Paranoid and delusional ideation
Hallucinations
Aggressiveness
Activity disturbances
Diurnal rhythm disturbances
Affective disturbances
Anxieties and phobias

[a]Based on Reisberg et al.[4]

of assessment is, however, subjective out of necessity. In order to assess efficacy in clinical trials in a valid and reliable manner, objective measures are required. These are provided by rating scales, such as the BEHAVE-AD.[4] The value provided by analysis of such scales allows comparison of the severity of the disorder and objective assessment of the effects of medications.

The BEHAVE-AD, CMAI,[5-7] and NPI[8,9] have been shown to be sensitive, valid, and reliable. BEHAVE-AD and CMAI have also been instrumental in demonstrating the efficacy of risperidone in the treatment of BPSD.[2,3]

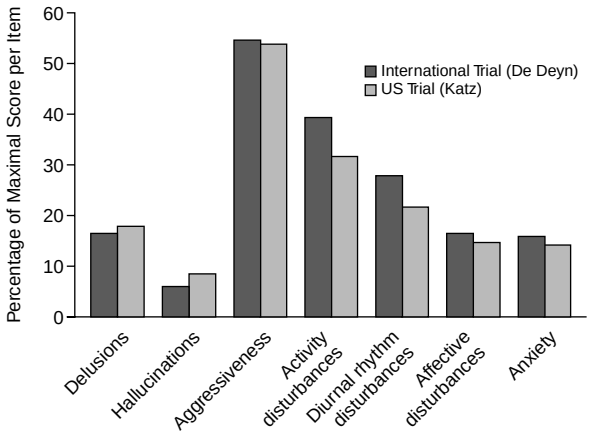
The BEHAVE-AD is a relatively simple scale that can be completed in a short period of time. It consists of 2 parts—symptomatology and global rating. The symptomatology section assesses 25 symptoms in 7 categories or clusters (Table 1). In the paranoid and delusional ideation cluster, for example, the scale examines the following symptoms: people are stealing things, one's house is not one's home, spouse (or other caregiver) is an impostor, delusion of abandonment, delusion of infidelity, suspiciousness/paranoia (other than above), and delusions (other than above).

Caregivers rate each item on a 4-point scale with reference to the patient's behavior over the preceding 2 weeks (0 = not present; 1 = present; 2 = present, generally with an emotional component; 3 = present, generally with an emotional and physical component). For example, for the delusion "one's house is not one's home" the scoring would be: 0 = not present; 1 = conviction that the place in which one is residing is not one's home; 2 = attempt to leave domicile to go home; and 3 = violence in response to attempts to forcibly restrict exit. The theoretical maximum possible score for the symptomatology is 75.

The second section of the BEHAVE-AD consists of a global assessment of the severity of BPSD by the caregiver, using the following ratings: 0 = not at all troubling to the caregiver or dangerous to the patient; 1 = mildly troubling to the caregiver or dangerous to the patient; 2 = moderately troubling to the caregiver or dangerous to the patient; 3 = severely troubling or intolerable to the caregiver or dangerous to the patient.

Figure 1 shows BEHAVE-AD data collected at baseline in 2 large-scale clinical trials.[2,3] It can be seen that, although the trials were conducted in different locations (United States and Canada/Europe, respectively), the enrolled patients with comparable baseline scores on the Mini-Mental State Examination had similar scores on each of the 7 clusters of the scale.[11] Similar profiles of BPSD in the studied populations were, therefore, demonstrated. It is notable that aggression was measured at about 60% of the maximal score, indicating an average rating of 6 on the aggressiveness cluster. The approximate percentages of maximal scores reached in the other 6 clusters of the BEHAVE-AD scale were as follows: activity disturbances (35%), diurnal rhythm disturbances (24%), delusions (17%), affective disturbances (16%), anxiety (15%), and hallucinations (7%).

Figure 1. Baseline Scores of the 7 BEHAVE-AD Clusters in 2 Large-Scale Trials[a]



[a]Data from De Deyn et al.[2] and Katz et al.[3]

Another important rating scale that has been used for the evaluation of treatments for BPSD is the CMAI, which looks at agitated behavior in patients with cognitive impairment. The CMAI is a 7-point rating scale that assesses the frequency with which patients manifest up to 29 agitated behaviors. It takes about 10 to 15 minutes to administer. Caregivers, who must be provided with appropriate training, rate the scale. The behaviors assessed by the CMAI are listed in Table 2. Each item is scored with reference to the preceding 2 weeks using the following ratings: 1 = never, 2 = < 1 time per week, 3 = 1–2 times per week, 4 = several times per week, 5 = once or twice per day, 6 = several times per day, and 7 = several times per hour. The theoretical maximum possible score is, therefore, 203.

The NPI assesses 12 behavioral disturbances common to dementia (Table 3). The severity and frequency of each of these behaviors are determined by a series of questions posed to the patient's caregiver. Severity is graded 1, 2, or 3 (mild, moderate, or severe) and frequency is rated 1–4 (1 = occasionally, less than once per week; 4 = very frequently, once or more per day or continuously). The maximum possible score for each domain is 12 (frequency × severity). Adding the scores for each indi-

Table 2. Behaviors Assessed by the Cohen-Mansfield Agitation Inventory (CMAI)[a]

1. Pacing, aimless wandering
2. Inappropriate dress or disrobing
3. Spitting (including at meals)
4. Cursing or verbal aggression
5. Constant unwarranted requests for attention or help
6. Repetitive sentences or questions
7. Hitting (including self)
8. Kicking
9. Grabbing onto people
10. Pushing
11. Throwing things
12. Strange noises (weird laughter or crying)
13. Screaming
14. Biting
15. Scratching
16. Trying to get to a different place (eg, out of the room, building)
17. Intentional falling
18. Complaining
19. Negativism
20. Eating/drinking inappropriate substances
21. Hurt self or other (cigarette, hot water, etc)
22. Handling things inappropriately
23. Hiding things
24. Hoarding things
25. Tearing things or destroying property
26. Performing repeated mannerisms
27. Making verbal sexual advances
28. Making physical sexual advances
29. General restlessness

[a]Based on Cohen-Mansfield,[5] Cohen-Mansfield et al.,[6] and Koss et al.[7]

Table 3. Behavioral Disturbances Assessed by the Neuropsychiatric Inventory (NPI)[a]

Delusions
Hallucinations
Agitation
Dysphoria
Anxiety
Apathy
Irritability
Euphoria
Disinhibition
Aberrant motor behavior
Nighttime behavior disturbances
Appetite and eating abnormalities

[a]Based on Cummings et al.[8] and Cummings.[9]

Table 4. Strengths and Weaknesses of the Extrapyramidal Symptom Rating Scale (ESRS)

Strengths
Exhaustive—single scale captures full range of treatment-emergent EPS
Well-anchored—valuable for the inexperienced user
Clear description of examination—increases interrater consistency
Weaknesses
Time-consuming—15 minutes, compared with 4–5 minutes for shorter instruments
Relative importance of syndromes is unstated—no indication of what to focus on during the examination
Overly sensitive when the entire scale is "collapsed" into a single summary variable—yields high rates of "placebo toxicity"

vidual domain derives a total NPI score. Caregivers are also asked to assess their own level of distress using a 6-point scale, where 0 is equivalent to no distress and 5 indicates very severe or extreme distress.[12] Again, the addition of scores for each behavioral domain gives a total distress score. The wide range of symptoms included within the NPI means that it is a useful tool for differentiating between dementias and for evaluating the efficacy of dementia treatments. Significant improvements in total NPI score were observed for dementia patients treated with risperidone[13] and cholinesterase inhibitors.[14,15] An abbreviated version of the test, the NPI-Q, has now been developed for use in routine clinical practice.[16]

It can be concluded that the efficacy of any new medication for BPSD can and should be assessed by applying these valid and reliable test instruments in randomized clinical trials.

SAFETY

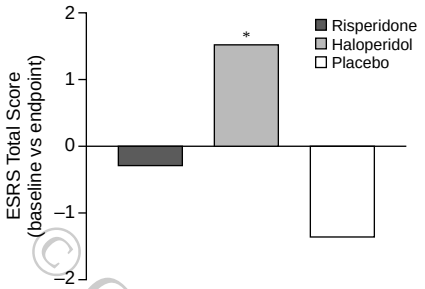
A number of rating instruments have been developed over the past 30 years to quantify aspects of EPS that occur following administration of antipsychotic agents. These EPS can be classified roughly into hypokinetic (i.e., parkinsonian), hyperkinetic (i.e., the various tardive syndromes), and restless (i.e., akathisia) domains.[17–21]

In general, the instruments constructed to assess EPS are designed to capture 1 or at most 2 of these 3 categories. These scales include the Simpson-Angus Scale, which measures the hypokinetic (parkinsonian) syndrome and is sometimes modified to include an item on akathisia,[22] the Barnes Akathisia Scale, which examines the subjective and objective components of akathisia,[23] and the Abnormal Involuntary Movement Scale, which measures tardive dyskinesia and is one of the most commonly used scales to assess EPS.[24]

The ESRS[10] attempts to bring some order to the relative chaos surrounding the scales used to assess extrapyramidal signs and symptoms, such as those mentioned above. The ESRS was designed to be inclusive. As well as measuring hypokinetic, hyperkinetic, and restlessness aspects of EPS, it also encompasses more unusual domains that are normally not considered in clinical trials. These include such syndromes as tardive dystonia, tardive tics, and others.

The ESRS is, therefore, an exhaustive 62-item instrument that is designed to capture virtually all aspects of treatment-emergent EPS. Because of its length and complexity, its use has been confined almost exclusively to clinical research trials. One of the problems for users new to the scale is that the total score does not indicate where the problems may lie. It is also not consistent in the ratings across the items—scores can range from 4 to 7. Many of the items (e.g., bradykinesia), but not all (e.g., difficulty in swallowing or talking), are anchored, with clear narratives. Table 4 presents a summary of the strengths and weaknesses of the ESRS.

Figure 2. Extrapyramidal Side Effects Resulting From Risperidone and Haloperidol[a]



[a]Data from De Deyn et al.[2] for change from baseline to endpoint.
Abbreviation: ESRS = Extrapyramidal Symptom Rating Scale.
*p < .05.

The ESRS is not straightforward and care should be taken in the interpretation of the scores it yields. Nevertheless, it is a highly sensitive, but successfully specific scale in separating neurotoxic medications from nontoxic agents. This function is illustrated by a recent, large, phase III clinical trial that compared risperidone with both placebo and the conventional neuroleptic haloperidol for treatment of BPSD.[2] After intention-to-treat analysis, endpoint ESRS scores for those patients assigned to risperidone were virtually unchanged from baseline values (Figure 2). In contrast, patients receiving haloperidol had a significantly increased ESRS score at endpoint. ESRS score was slightly reduced at endpoint among patients in the placebo group.

CONCLUSION

As more modern pharmacologic treatments for BPSD have become available, reliable, well-validated, and easily applicable scales for assessing their efficacy and safety have become increasingly important. The BEHAVE-AD was designed to examine the behavioral symptoms of Alzheimer's disease in both prospective studies and trials of pharmacologic agents. The scale measures the severity of symptoms in 7 specific behavioral "clusters" and allows a global rating. The CMAI evaluates agitated behavior in patients with cognitive impairment. It is a 7-point rating scale assessing the frequency with which patients manifest 29 agitated behaviors. A further scale, the NPI, embraces a somewhat wider range of psychopathology and may help to distinguish between different causes of dementia. With regard to safety, a variety of scales have been developed to monitor EPS, the most comprehensive of which is the ESRS.

Drug names: haloperidol (Haldol and others), risperidone (Risperdal).

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