



**International  
Psychogeriatric  
Association**

550 Frontage Road, Suite 2820  
Northfield, IL 60093 USA  
☎ 1+847.784.1701  
Fax 1+847.784.1705  
E-mail ipa@ipa-online.org  
Web site www.ipa-online.org

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February 17, 2000

Dockets Management Branch  
FDA  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Docket 00N – 0088

The enclosed is a submission from the International Psychogeriatric Association (IPA) in response to the “Division of Neuropharmacological Drug Products (DNBP) Issues Paper for March 9, 2000 Meeting of the Psychopharmacological Drugs Advisory Committee Meeting on the Various Psychiatric and Behavioral Disturbances Associated with Dementia.”

Please post for Docket 00N – 0088. An electronic copy has been sent to Sandra Titus.

We hope that Dr. Sanford Finkel will have the opportunity to present the position of IPA in person at the meeting.

We thank you for your assistance. Please let us know if there is any thing additional needed.

Sincerely,

Fern F. Finkel  
Executive Director

00N-0088

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THE INTERNATIONAL PSYCHOGERIATRIC ASSOCIATION  
RESPONSE TO THE DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
(DNDP) ISSUES PAPER  
for the March 9, 2000 Meeting of the  
Psychopharmacological Drugs Advisory Committee Meeting on the  
Various Psychiatric and Behavioral Disturbances Associated with Dementia.

This response presents views from a wide cross-section of physicians, other health care professionals and scientists who have special interest and expertise in the area of psychiatric and behavioral disturbances associated with dementia. The participants of two international consensus conferences, held under the auspices of the International Psychogeriatric Association (IPA), concluded that an umbrella term is needed to describe the array of symptoms found in Alzheimer's disease. **The consensus term, "behavioral and psychological symptoms of dementia" (BPSD) was and is meant to function as an umbrella term, and not necessarily as a definition of a discrete clinical condition.**<sup>1,2</sup> This presentation focuses on why and how experts arrived at this term, its usefulness and limitations, and how this information may be applicable for clinical trials.

The FDA indicates that one of the criteria for determining a psychosis of Alzheimer's disease or for that matter any clearly delineated syndrome associated with dementia is that it must be "accepted in the relevant clinical/academic community"<sup>3</sup>. We propose that the International Psychogeriatric Association (IPA) with its consensus conferences and outcome recommendations has taken important initial steps toward fulfilling that criterion. IPA is the largest international organization dedicated to the mental health of the elderly. It represents thousands of health care professionals, researchers, and scientists from 62 countries, many of whom are leading researchers and clinicians in their regions and countries as well as worldwide. The largest membership constituency is American. Its members include psychiatrists, neurologists, geriatricians, internists and family practitioners, psychologists, nurses, and others.

In 1993, aware of the rapid growth of demented elderly worldwide and the devastation wrought by what was then known as the "behavioral disturbances of dementia (BDD)", IPA established a task force to focus attention and enhance research and educational activities in this area of growing importance. It has been clear that this array of symptoms is responsible for increased rates of hospitalizations and premature nursing home placements, causes suffering for patients and caregivers alike, and is a growing burden economically for the United States and other countries<sup>4,5,6,7</sup>. We elucidated the existing research methodology for conducting clinical trials<sup>8</sup> in this area and noted several marked changes.

First, the field was growing rapidly. Prior to 1990, only 7 double-blind, placebo-controlled studies of anti-psychotics for demented elderly existed in the worldwide literature<sup>9</sup>. Yet in the 1990s, we were witnessing a substantial increase in clinical drug trial activity for "psychiatric

and behavioral disturbances” in demented elderly. Anti-psychotic research includes multi-site studies of risperidone (3 studies)<sup>10,11</sup>, olanzapine (2 studies)<sup>12,13</sup> and quetiapine. Moreover, single-site, placebo-controlled, double-blind studies have been conducted on thiothixene<sup>14</sup>, and haloperidol<sup>15</sup>. These studies have focused on psychotic symptoms, but also on related symptoms found in Alzheimer’s disease, including agitation, sleep abnormalities, depressive symptoms, and abnormal behavioral symptoms.

Additional studies utilizing drugs not commonly associated with anti-psychotic qualities have been or are being conducted with valproic acid (2 studies — one on mania of dementia, one on agitation), sertraline, fluoxetine (in comparison with haloperidol and thioridazine, as well as placebo), buspirone and carbamazepine<sup>16</sup>. Thus, the FDA’s current initiative to attempt to clarify the definition and methodology of clinical trials in this area is especially timely. IPA has played a special role in conceptualizing these clinical drug trials. The largest studies were designed and conducted following 2 days of intensive consultation with the IPA Task Force. Further, IPA members played a significant role in virtually all of the above studies.

Secondly, the definition “behavioral disturbances of dementia” was vague from both a clinical perspective and a measurement and scale perspective. Prior to 1985 there was no single measurement or scale developed for “psychiatric and behavioral disturbances associated with dementia”. By 1996 there were 16<sup>8</sup> and currently there are over 30 that address aspects of these “disturbances”. With no clearly accepted clinical criteria and no measurement or scale agreed upon as a gold standard, it became clear that those clinicians and researchers actively working in this area needed to assemble to define what we were studying.

Thus, on March 31-April 2, 1996, experts from 16 countries assembled in the Washington, DC area to arrive at a consensus as to what it was we were studying, as well as to establish a research agenda. Expert researchers and clinicians worldwide presented their research on etiology, nomenclature, scales and measurements, the wide range of symptoms, potential syndromes, pharmacological and non-pharmacological studies, criterion validity, caregiver issues, cross-cultural and trans-national considerations and an agenda for further research. (See Appendix A for agenda of the meeting and participants). Several presented data supporting the position that many of these symptoms have neuropathologic and neurochemical etiologies<sup>17,18,19,20</sup>, an issue highlighted in the DNDP paper.

All participants agreed that we needed a broad umbrella term that was inclusive of the considerable variety of symptoms found in this population, and that subsequent steps could be geared at studying and clustering symptoms in order to determine whether discrete syndromes were identifiable. The virtual unanimous agreement was that the term *behavioral disturbances of dementia* was an unsatisfactory umbrella term. Many of the experts objected to use of this term, stating that hallucinations, delusions, depression, etc., were not really *behavioral disturbances*. Further, the term *disturbance* was considered too vague, and the participants could not agree on a standard definition. Other umbrella terms were considered, but were rejected. For example, *non-cognitive symptoms* was not accepted. If a person could not find his/her wallet and became paranoid that a caregiver stole it, was this symptom completely non-cognitive? The

group thought not. The term *neuro-psychiatric symptoms* was also not accepted with the objection that many of the symptoms were not viewed as neurological. Ultimately, the consensus was that the most accurate, descriptive term was the “behavioral and psychological signs and symptoms of dementia”<sup>21</sup>, later shortened to “behavioral and psychological symptoms of dementia (BPSD), a term used to describe a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors occurring in people with dementia”<sup>2</sup>.

After a substantial increase in research and clinical activities between 1996 and 1999, IPA held a second consensus conference, May 11-13 1999, to update the developments of the prior three years and to prepare a new research agenda (See Appendix B for participants and program). Sixty-one (61) participants from 17 countries and representing 9 disciplines attended. Additional evidence was presented correlating certain depressive and psychotic symptoms with neuropathologic changes and genetic polymorphisms<sup>22,23</sup>. The participants also re-affirmed the usefulness of BPSD as a broad, descriptive term.

From a drug regulatory standpoint, the FDA position paper correctly points out the limitations of the term BPSD: “While the concept BPSD acknowledges and focuses attention on this important aspect of dementia, and identifies dementia as a population with possibly unique psychiatric disturbances, the Agency has considered this too broad a target. It refers to multiple clinical entities. It contains unique and heterogeneous psychiatric disturbances, some of which remain to be defined. Since it is unclear which of these many clinical conditions would be responsive to treatment, the Agency has considered the use of BPSD in labeling potentially misleading.”

However, the participants at the first IPA consensus conference agreed that BPSD would be a useful, general, initial umbrella term, which would be all-inclusive, and from which we could try to sort and categorize symptoms into discrete syndromes. Indeed this has been evolving. Hope, et al., based on their research, have proposed several discrete syndromes, including a psychosis, a delirium and a behavioral syndrome. McShane<sup>24</sup> has developed these ideas further. Moreover, as a result of work that grew out of the IPA 1999 Conference, Finkel and Jeste<sup>25</sup> have proposed a psychosis specific to Alzheimer’s disease (2000). This psychosis is different from the psychosis of schizophrenia in the realms of general epidemiology, associated morbidity and risk factors, types and severity of clinical symptoms, duration of illness, dosages of medication required, and side effects of medication prescribed.

**IPA supports these proposed criteria for the psychosis of Alzheimer’s disease. The prevalence, incidence, the neurochemical and neuropathological correlates, the clinical characteristics that are common at various stages of the disease, and the treatment responses all argue for this discrete clinical condition.**

Now that a psychosis of Alzheimer’s disease has been proposed, it is also appropriate to examine the special characteristics of depression in dementia, as well as the characteristics of anxiety and circadian rhythm abnormalities. IPA supports the FDA position that each condition needs further investigation and clarification to determine whether it meets the other FDA criteria of being “operationally definable” in a “reasonably homogeneous patient group”. Thus,

further research must include a sub-clustering of the symptoms currently identified to determine the viability of clinical trials, both pharmacological and non-pharmacological, in any other discrete clinical conditions found in and unique to Alzheimer's disease.

Although no current medication can claim to treat the whole range of symptoms characterized under the umbrella term, BPSD, this does not mean that a medication may not alleviate more than the specific psychotic symptoms.

For example, Haloperidol is indicated for use in the management of manifestations of psychotic disorders<sup>26</sup>. This usually denotes gross thought disorder, including hallucinations and delusions. However, the diagnosis can be made without delusions or hallucinations. Among the symptoms commonly associated with schizophrenia are bizarre behavior, illogicality, pressure of speech, avolition, anhedonia, alogia and affective flattening<sup>27,28</sup>. In fact, the Flexible System, derived from the International Pilot Study of Schizophrenia required between 4 to 8 of 12 possible discriminators to establish a diagnosis of schizophrenia. This heterogeneous grouping includes restricted affect, poor insight, hearing thoughts aloud, absence of early awakening, poor rapport, absence of depressed facies, absence of elation, widespread delusions, incoherent speech, unreliable information, bizarre delusions, and nihilistic delusions<sup>29</sup>.

Are all distinct symptoms treatable by the same drug? Some medications may be effective at reducing or eliminating what are commonly called the "positive symptoms of schizophrenia" whereas other medications have been shown to reduce both the positive and negative symptoms of schizophrenia.

Similarly, Alzheimer's disease and other dementias contain a range of symptoms, which include delusions, hallucinations, agitation and aggressive behavior, sleep abnormalities, depressive symptoms, apathy, and anxiety. Some anti-psychotic medications may specifically control the delusions, hallucinations and aggressive behavior that generally represent the most significant symptoms of Alzheimer's psychosis. Yet, it is possible — even likely — that medications may reduce or eliminate many of the other associated symptoms as well. The IPA agrees that patients who suffer from the psychosis of Alzheimer's disease must be identified primarily by their psychotic symptoms. However, patients and their families, the professional community and lay public, would benefit in knowing what associated symptoms — for example, agitation, anxiety, depression and sleep abnormalities, in addition to the psychotic symptoms — can be alleviated by psychoactive medication.

IPA strongly supports the need for labeling in this area. Current estimates are that more than 2/3 of all Alzheimer's patients experience delusions and/or hallucinations over the course of their illness. Yet, without labeling, many of these patients receive medication on an ad hoc basis. Physicians do not have guidelines on when and when not to prescribe these medications, which ones are associated with greater or fewer risks in this vulnerable population, and what dosing can be expected to be the most effective and safest.

IPA has an additional concern. Because of its regulatory role the FDA may have significant impact on the labeling policies for other countries, including developing countries. Others look to FDA for leadership and guidance, and their own policies often follow FDA policies. As the number of demented people increase world-wide, and those with psychosis of Alzheimer's disease and other clinical conditions grow commensurately, the importance of an FDA policy on labeling takes on growing significance.

IPA supports the FDA's initiative in bringing attention to this area, and supports the requirement that clinical illnesses must be operationally defined and accepted by the academic community. Indeed, with broad representation within the professional/academic community and more than seven years of concentrated support of these goals, IPA is in a unique position on this matter and can be helpful to the FDA in a variety of ways (for example, providing additional clarification and definition of the conditions to be studied, expansion on the etiologic factors, review of the instruments that are most appropriate for these studies, and the design of clinical trials to test efficacy and safety of medications). We welcome the opportunity for future collaboration to assist the FDA in bringing greater clarification and direction and furthering progress in this important area.

Sincerely,

Sanford I. Finkel, MD,  
Chair, IPA Task Force on Behavioral and Psychological Symptoms of Dementia

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Pierre Tariot, MD  
Rochester, NY USA

Michael Zaudig, M.D.  
Germany

## Appendix A

# International Psychogeriatric Association Consensus Conference on Behavioral Disturbances of Dementia March – April, 1996

## **I. Introduction**

- A. New Focus on Behavioral and Psychological Signs and Symptoms of Dementia S. Finkel (USA)
- B. Consensus Conference Goals and Objectives B. Lebowitz (USA)

## **II. Etiology**

- A. Clinicopathologic and Neurochemical Correlates of Major Depression and Psychosis in Primary Dementia G. Zubenko (USA)
- B. Neurochemistry and Neurotransmitters C. Gottfries (Sweden)
- C. Neuropathology of Psychotic Symptoms in Alzheimer's Disease W. Bondareff (USA)
- D. Neuroimaging and the Origin of Psychiatric Symptoms in Dementia D. Sultzer (USA)
- E. Circadian Rhythm-Related Behavioral Disturbances and Structural Hypothalamic Changes in Alzheimer's Disease W. Hoogendijk (Netherlands)
- F. Self-Psychology: Its Application to Understanding Patients with Alzheimer's Disease L. Lazarus (USA)
- G. Environmental and Social Aspects of Behavioral Disturbances in Dementia B. Lawlor (Ireland)
- H. Behavioral Disturbances of Dementia and Caregiver Issues S. Zarit (USA)
- I. Discussion All

## **III. BDD In Our Current Nomenclature System**

- A. Diagnostic Classification of Neuropsychiatric Signs and Symptoms in Patients with Dementia E. Caine (USA)
- B. Behavioral Disturbances of Dementia: Practical and Conceptual Issues P. Rabins (USA)
- C. Behavioral Disturbances of Dementia in DSM-IV and ICD-10: Fact or Fiction M. Zaudig (Germany)
- D. Discussion All

## **IV. Theory Behind Scales and Measurements**

- A. Theories Behind Existing Scales for Rating Behavior in Dementia J. Cummings (USA)
- B. Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Rating Scale B. Reisberg (USA)
- C. Conceptualization of Agitation: Results Based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument J. Cohen-Mansfield (USA)
- D. CERAD Behavior Rating Scale for Dementia P. Tariot (USA)
- E. Caretaker Obstreperous Behavior Rating Scale J. Swearer (USA)
- F. Dementia Behavior Disturbance Scale S. Gauthier (Canada)
- G. Dementia Mood Assessment Scale T. Sunderlund (USA)
- H. Dysfunctional Behavior Rating Instrument D. Molloy (Canada)
- I. Direct Observation of Behavioral Disturbances of Dementia and Their Environmental Context L. Burgio (USA)
- J. Selecting Outcome Measures for Clinical Trials of BDD L. Teri (USA)
- K. Discussion All

## **V. Criterion Validity: Do the Symptims Respond to Treatment –Pharmacologic and/or Nonpharmacologic?**

- A. Antipsychotic Treatment in Outpatients with Dementia D. Devanand (USA)

- B. Behavioral Symptoms in Dementia: Community Based Research S. Auer (USA)
- C. Nursing Home Research from Industry's Perspective M. Brecher (USA)
- D. Nursing Home Research from Investigators' Perspective J. Lyons (USA)
- E. Meta-Analysis of Controlled Pharmacologic Trials L. Schneider (USA)
- F. Discussion All

**VI. Clinical Perspectives: What Should We Be Studying?**

- A. Delusions M. Trabucchi (Italy)
- B. Hallucinations P. Whitehouse (USA)
- C. Misidentification A. Burns (USA)
- D. Agitation, Wandering, Pacing, Restlessness, and Repetitive Mannerisms A. Siegel (USA)
- E. Disinhibition, Apathy, Fatigability, Complaining, and Negativism G. Grossberg (USA)
- F. Emotional Lability, Intrusiveness, and Catastrophic Reactions M. Haupt (Germany)
- G. Depression, Anxiety, and Sleep Disturbances B. Reifler (USA)
- H. Falling, Hoarding, Hiding, Eating Disturbances, and Sexual Disinhibition B. Brannstrom (Sweden)
- I. Discussion All
- J. Differentiating BDD from Symptoms of Delirium J. Luxenberg (USA)
- K. Differentiating BDD from Drug Side Effects of D. Jeste (USA)
- L. BDD in the Nursing Home B. Rovner (USA)
- M. BDD in Ambulatory Care Settings K. Ritchie (France)
- N. Vascular Dementia vs. Alzheimer's Disease – Should We Be Studying Both Within the Same Study? S. Eriksson (Sweden)
- O. Discussion All

**VII. What Aspects of BDD are Important to Caregivers?**

- A. Perspectives of a Family Caregiver S. Kenowsky (USA)
- B. Caregivers and Behavioral Disturbances: Effects and Interventions H. Brodaty (Australia)
- C. Perspectives of an Institution-Based Research Nurse A. Norberg (Sweden)
- D. Perspectives of a Clinical Trials Research Nurse C. Cooler (USA)
- E. Discussion All

**VIII. Cross-Cultural Perspectives**

- A. Argentina C. Mangone (Argentina)
- B. India V. Chandra (India)
- C. Caribbean, Native American and Yoruba H. Hendrie (USA)
- D. Agitation in Demented Patients in the United States J. Mintzer (USA)
- E. Discussion All

**IX. Research**

- A. Future Research Directions Z. Khachaturian (USA)

**X. Consensus Statement**

- A. Behavioral and Psychological Signs and Symptoms of Dementia: A Consensus Statement on Current Knowledge and Implications for Research and Treatment

By: Sanford I. Finkel (USA), Jorge Costa e. Silva (Brazil), Gene Cohen (USA),  
Sheldon Miller (USA), & Norman Sartorius (Switzerland)

**Behavioral and Psychological Symptoms of Dementia (BPSD):  
A Clinical and Research Update  
May 1999**

**I. Perspectives of BPSD**

**Moderated by:**

- A. BPSD in DSM IV and beyond
- B. BPSD in ICD 11
- C. Epidemiology of BPSD
- D. BPSD and quality of life
- E. BPSD in nursing home residents: the economic implications
- F. How do BPSD predict institutionalization?
- G. Are BPSD associated with mortality?
- H. The importance of BPSD in primary care

**S. Finkel (USA)**

- E. Caine (USA)
- M. Zaudig (Germany)
- D. O'Connor (Australia)
- P. Rabins (USA)
- J. O'Brien (USA)
- G. Grossberg (USA)
- D. Gilley (USA)
- W. Coleman (USA)

**II. Etiology**

**Moderated by:**

- A. Neuropathology of BPSD
- B. The contribution of genetics to understanding BPSD
- C. The impact of the environment on BPSD
- E. The impact of BPSD on caregivers
- E. The impact of personality on BPSD

**A. Burns (UK)**

- H. Forstl (Germany)
- C. Holmes (UK)
- S. Eriksson (Sweden)
- C. Ballard (UK)
- W. Meins (Germany)

**III. Phenomenology**

**Moderated by:**

- A. Delusions and hallucinations
- B. Physical aggression and catastrophic reactions
- C. Physical non-aggressive agitation
- D. Depression in BPSD
- E. Apathy and withdrawal
- F. Anxiety in BPSD
- G. Circadian rhythms and BPSD
- H. What are the syndromes of BPSD?
- I. Is BPSD a distinct syndrome?
- J. What is the relationship between cognition and BPSD?

**M. Zaudig (Germany)**

- S. Holroyd (USA)
- I. Katz (USA)
- M. Haupt (Germany)
- F. Verhey (Netherlands)
- S. Starkstein (Argentina)
- J. Mintzer (USA)
- D. Bliwise (USA)
- R. McShane (UK)
- B. Reisberg (USA)
- G. Swanwick (Ireland)

**IV. Diagnosis/Assessment**

**Moderated by:**

- A. What has changed in clinical assessment of BPSD?
- B. New and promising assessment modalities
- C. Neuroimaging
- D. BPSD and Frontal Lobe Dementia
- E. BPSD and Lewy Body Dementia
- F. BPSD and Vascular Dementia
- G. BPSD and Delirium
- H. What are the necessary characteristics of a BPSD rating scale?

**M. Haupt (Germany)**

- M. Trabucchi (Italy)
- I. Monteiro (USA)
- J. Luxenberg (USA)
- A. Kertesz (Canada)
- I. McKeith (UK)
- T. Erkinjuntti (Finland)
- J. Lindesay (UK)
- A. Shah (UK)

**V. Pharmacological approaches – what is the role of medication in the treatment of BPSD?**

**Moderated by:**

**A. Burns (UK)**

- |  |                      |
|--|----------------------|
| A. What are the characteristics of the ideal drug for BPSD?                            | D. Jeste (USA)       |
| B. Brain morphologic and neurochemical correlates of depression in Alzheimer's disease | G. Zubenko (USA)     |
| C. Cholinergic contributions to BPSD   | T. Sunderland (USA)  |
| D. Anti-convulsants  | P. Tariot (USA)      |
| E. SSRIs and Trazodone in the treatment of BPSD  | D. Sultzer (USA)     |
| F. Conventional neuroleptics in the treatment of BPSD                                  | D. Devanand (USA)    |
| G. Risperidone in the treatment of BPSD  | P. De Deyn (Belgium) |
| H. Other novel anti-psychotics   | M. Davidson (Israel) |
| I. Anxiolytics in the treatment of BPSD  | H. Allain (France)   |
| J. Hormonal treatments for BPSD  | G. Small (USA)       |
| K. What has changed in clinical trials of BPSD?  | S. Finkel (USA)      |
| L. Do we need a meta-analysis update?  | L. Schneider (USA)   |

**VI. Regulatory Issues**

**Moderated by:**

**P. Whitehouse (IWG)**

The International Working Group of Harmonization of Dementia Drug Guidelines (IWG) will be organizing the component

- |  |                     |
|--|---------------------|
| A. Regulatory Issues on BPSD – an Overview | P. Whitehouse (USA) |
| B. Regulatory Issues on BPSD in Europe     | I. McKeith (UK)     |
| C. Regulatory Issues on BPSD in Japan      | A. Homma (Japan)    |
| D. Regulatory Issues on BPSD in the USA    | T. Laughren (USA)   |

**VII. Non-pharmacological management and treatment**

**Moderated by:**

**S. Finkel (USA)**

- |  |                          |
|--|--------------------------|
| C. Impact of caregiver interventions and support groups on BPSD                    | M. Mittelman (USA)       |
| B. Caregiver burden  | A. Burns (UK)            |
| C. Application of psychosocial interventions for treating BPSD                     | L. Burgio (USA)          |
| D. Music, art, and recreation therapies in the treatment of BPSD                   | L. Gerdner (USA)         |
| E. Day care centers in the management of BPSD.                                     | N. Jorgensen (Spain)     |
| F. The use of patient characteristics to determine non-pharmacologic interventions | J. Cohen-Mansfield (USA) |
| G. Combined therapy: an overview   | L. Teri (USA)            |

**VIII. Cross-cultural and trans-national issues**

A. Translations of measurements and scales: opportunities and diversities

S. Auer (Germany)

B. Racial differences in BPSD

C. Cohen (USA)

C. BPSD in Africa and the Caribbean

H. Hendrie (USA)

D. BPSD in Eastern and South Eastern Europe and the Middle East

E Eker (Turkey)

E. BPSD in Latin America

D. Resnikoff

F. BPSD in Japan and the Asian Pacific Region

Presenting for C. Mangone (Argentina)

A. Homma (Japan)

**XI. Recommendations**

A. Recommendations on Diagnosis and Assessment

A. Burns

B. Recommendations on Pharmacological Treatment

G. Cohen

C. Recommendations on Non-pharmacological Treatment

G. Cohen

D. Recommendations for Research Agenda

E. Caine

E. Conclusions

S. Finkel/A. Burns

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