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Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus

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ABSTRACT

Objectives: Behavioral and psychological symptoms of dementia (BPSD) are nearly universal in dementia, a condition occurring in more than 40 million people worldwide. BPSD present a considerable treatment challenge for prescribers and healthcare professionals. Our purpose was to prioritize existing and emerging treatments for BPSD in Alzheimer's disease (AD) overall, as well as specifically for agitation and psychosis.

Design: International Delphi consensus process. Two rounds of feedback were conducted, followed by an in-person meeting to ratify the outcome of the electronic process.

Settings: 2015 International Psychogeriatric Association meeting.

Participants: Expert panel comprised of 11 international members with clinical and research expertise in BPSD management.

Results: Consensus outcomes showed a clear preference for an escalating approach to the management of BPSD in AD commencing with the identification of underlying causes. For BPSD overall and for agitation, caregiver training, environmental adaptations, person-centered care, and tailored activities were identified as first-line approaches prior to any pharmacologic approaches. If pharmacologic strategies were needed, citalopram and analgesia were prioritized ahead of antipsychotics. In contrast, for psychosis, pharmacologic options, and in particular, risperidone, were prioritized following the assessment of underlying causes. Two tailored non-drug approaches (DICE and music therapy) were agreed upon as the most promising non-pharmacologic treatment approaches for BPSD overall and agitation, with dextromethorphan/quinidine as a promising potential pharmacologic candidate for agitation. Regarding future treatments for psychosis, the greatest priority was placed on pimavanserin.

Conclusions: This international consensus panel provided clear suggestions for potential refinement of current treatment criteria and prioritization of emerging therapies.

Key words: dementia, behavioral, psychosis, treatment, consensus, Delphi

Introduction

There are more than 40 million people with dementia worldwide, of whom the majority have Alzheimer's Disease (AD) (Alzheimer's Disease International, 2010). More than 90% of people with dementia will experience behavioral and psychological symptoms of dementia (BPSD), such as agitation, aggression and psychosis, during the course of their dementia (Ballard and Corbett, 2013). Agitation and aggression occur in approximately 20% of people with AD in contact with clinical services or living in the community (Fossey *et al.*, 2006; Chenoweth *et al.*, 2009). A higher prevalence is seen in residential care facilities due to the higher level of cognitive impairment in residents, with BPSD affecting 40% to 60% of individuals in these settings (Fossey *et al.*, 2014). Psychosis, defined by the emergence of delusions and hallucinations, is somewhat distinct from other BPSD, and occurs in 20% of people. Of the myriad symptoms presenting

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in AD, BPSD are among the most distressing for individuals and their carers, often leading to considerable stress and mental health issues such as depression in caregivers (Ballard and Corbett, 2010). BPSD are also strongly correlated with reduced quality of life and are a common trigger for institutionalization (Corbett *et al*., 2013). The development, evaluation, and implementation of therapies to improve the treatment and care of BPSD is therefore a high priority.

Existing best practice guidelines for the management of BPSD consistently promote non-pharmacological interventions as the first-line approach for treatment, particularly for agitation and aggression, and there is a growing evidence base to support the value of this approach. However, there is an emerging evidence base that indicates that non-drug approaches exert a differential impact on psychosis and agitation, and that the selection of these approaches is critical to ensure a beneficial outcome (Testad *et al*., 2014).

BPSD present a considerable treatment challenge for prescribers and healthcare professionals. They have often traditionally been treated pharmacologically with atypical antipsychotic medications. There is evidence to support modest symptomatic benefit of short-term treatment with atypical antipsychotics, particularly risperidone, olanzapine and aripiprazole, which are linked to a standardised effect size of 0.2. However, this evidence is limited to treatment of severe aggression that has not resolved through alternative pharmacological or non-drug approaches. Risperidone and aripiprazole also appear to confer similar modest benefits for the treatment of psychosis. Benefits to non-aggressive agitation and longer term treatment are less clear. Unfortunately, the modest benefits associated with antipsychotics must be balanced against significant safety concerns including accelerated cognitive decline, stroke, and death, particularly when used in the long term (Kales *et al*., 2015; Maust *et al*., 2015). Risperidone is licensed in the European Union and Australia, but not in the United States, for the short-term treatment of aggression in people with AD. Therefore, whilst non-pharmacological strategies provide a useful first line treatment approach, there is an urgent need for more effective and safer pharmacological interventions which confer longer term benefits.

Until recently there was limited evidence to inform the potential use of other pharmacological treatments, with the exception of several studies suggesting the absence of benefits with valproic acid and trazodone. More recently, the field has expanded significantly. In addition to emerging evidence from small studies of carbamazepine, oxycarbazine and prazosin, recent larger RCTs of dextromethorphan, citalopram, stepped analgesia, and larger trials of non-pharmacological interventions have begun to provide a more informative evidence base, with further small RCTs and secondary analyses identifying additional potential candidates.

We are therefore entering encouraging but new territory, where it will become increasingly important to prioritize emerging treatments both in terms of further research and potential clinical use. The Delphi consensus process is an established process by which expert opinion can be sought and refined to answer pressing questions relating to specific clinical questions. Given the importance of the issue, and in the context of newly emerging evidence, the management of BPSD in AD, specifically agitation and psychosis, is a timely and high priority topic for a consensus finding study. This paper describes a modified Delphi consensus study, which sought to prioritize non-pharmacological, pharmacological, and emerging treatments both overall and for agitation and psychosis in people with AD.

Methods

Design

This study utilized a modified Delphi consensus approach to identify the most effective current non-pharmacological and pharmacological treatments, and the most promising emerging interventions for overall BPSD, as well as those specifically for agitation and psychosis in AD. Delphi consensus protocols provide a structured, anonymized approach to gathering and refining expert opinion relating to a specific question, as moderated by a facilitator. This process involves at least two rounds of input from an expert group, who provide informed opinions that are filtered and reassessed until a consensus is reached. This study adapted the standard Delphi approach, for which the protocol and number of rounds were defined *a priori*. Two rounds of feedback were conducted through an online survey, followed by a third round which was conducted as an in-person meeting to ratify the outcome of the electronic process. This latter step was taken to allow for more detailed discussion, which was not felt to be feasible through email and commenting.

Expert panel participants

The expert panel consisted of 11 panelists from a variety of geographic locations including Europe, the United States, the United Kingdom, Australia, and Canada. Each expert panel member was required to have clinical expertise in the

management of BPSD and research expertise as evidenced by a significant research publication record in work related to BPSD.

Delphi round 1: capturing current and future treatment candidates for BPSD

During the first round of the Delphi process expert panel members were contacted by email and asked to complete an online survey. They were asked to provide an open list of current pharmacological and non-pharmacological treatments that they felt were most effective and appropriate for the treatment of BPSD in AD. They were also asked to suggest experimental and future approaches, both pharmacological and non-pharmacological, which they believed were most promising. Thus, they were providing responses to four categories of treatments; current pharmacologic, current non-pharmacologic, future/experimental pharmacologic, and future/experimental non-pharmacologic. Members were asked to include only approaches with at least one published clinical trial that suggested benefit to the target population, and were asked to include references to support their statements. A facilitator compiled the outputs of the first round, along with the relevant literature, and refined them for compliance with the stipulated requirements. Candidate treatments were removed if they did not comply with the criteria of one published supporting clinical trial. The responses were then grouped by category and combined with published references to create a comprehensive report for each.

Delphi round 2: prioritization of identified items

Once the comprehensive lists of treatments for each category were compiled, the expert panel members were again contacted by email and asked to complete a second more specific online survey. They were provided with a full list of all eligible candidate treatments for the four categories. The panel members were asked to rank their five preferred current treatments by assigning a rank of 1 to the highest priority treatment, rank of 2 for their second highest priority treatment, and so on. For current treatments, they were asked to rank both pharmacological and non-pharmacological treatments together in the same list to provide a clear indication of how these two categories might be used together as well as how they compared to one another. In addition, the panelists were asked to rank their five preferred future treatments, separately for pharmacologic and non-pharmacologic this time, using the same process. Finally, they were asked to list their preferred first and second line treatments for the specific behaviors of agitation and psychosis in three categories; current treatments (both pharmacologic and non-pharmacologic), future pharmacologic, and future non-pharmacologic.

The responses were again collated and analyzed by the facilitator. Treatments were allocated weighted scores dictated by the rank given by the panel members, and presented as a ranked list for current treatments (pharmacological and non-pharmacological combined), future pharmacological, and future non-pharmacological. The same process was completed with candidate treatments for psychosis and agitation. Candidates were removed at this stage if they had not been ranked by at least two panel members. The remaining ranked lists were prepared as a report for the third stage.

Delphi round 3: in-person prioritization meeting

Panel members attended a prioritization meeting at the International Psychogeriatric Association's International Congress in Berlin in October 2015. Prior to the meeting, all members received a full packet containing the list of ranked candidates for all categories, including the specific lists for agitation and psychosis, and the supporting evidence. The purpose of the meeting was to discuss the rankings and to refine the list of treatments further. The objectives of the study were reviewed and the progress to date discussed, with a focus on addressing any discrepancies between candidates, in order to reach a consensus. The meeting was audio recorded and detailed notes were taken during the discussion. The audio recording was later used as needed for clarity. At the end of the meeting, each panel member was asked to provide a final ranking of their top five candidates for each category based on their interpretation of the discussion. The overall ranking list was then adjusted for the new ranks, and any items not prioritized by at least two panel members and included in at least one clinical trial were excluded.

Delphi consensus criteria

For this study, consensus was defined as percentage agreement across the expert panel members following the third round of prioritization. The top three treatments required at least a 70% agreement within a range of one rank score across the panel for consensus to be ratified. Treatments accepted into the remaining priority list required at least 60% agreement within a range of one rank score across the panel. The study stopping criterion was completion of the four rounds as defined in the protocol.

Table 1. Delphi consensus expert panel members

NAME	AFFILIATION	CREDENTIALS
Clive Ballard, MD	University of Exeter	Geriatric Psychiatrist
Sube Banerjee, MD*	Brighton and Sussex Medical School, University of Sussex	Geriatric Psychiatrist
Henry Brodaty, MD	Centre for Healthy Brain Ageing (CHeBA), UNSW Australia	Psychogeriatrician
Claudia Cooper, PhD	Division of Psychiatry, University College of London, UK	Geriatric Psychiatrist
Lutz Froelich, MD, PhD	Department of Geriatric Psychiatry, Central Institute of Mental Health Medical Faculty Mannheim, University of Heidelberg, Germany	Geriatric Psychiatrist
Serge Gauthier, MD	McGill University	Neurologist
Helen C. Kales, MD	University of Michigan	Geriatric Psychiatrist
Ann Kolanowski, PhD, RN	Pennsylvania State University	Neurobehavioral nursing research
Constantine G. Lyketsos, MD	Johns Hopkins University	Geriatric Psychiatrist
Jacobo Mintzer, MD, MBA	Roper St. Francis Clinical Biotechnology Research Institute and Medical University of South Carolina (MUSC)	Geriatric Psychiatrist
Philippe Robert, MD, PhD*	University of Nice Sophia Antipolis	Psychogeriatrician
Geir Selbaek, MD, PhD	University of Oslo	Old Age Psychiatrist
Sytse Zuidema, MD	University of Groningen, University Medical Center Groningen, the Netherlands	Geriatrician

*Were unable to attend the in person prioritization.

Results

Delphi panel participants

A total of 14 individuals were invited to contribute to the Delphi consensus study, of whom 13 agreed to participate, and 11 attended the in-person prioritization meeting. Their names, credentials, and affiliations are provided in Table 1. Panelists represented specialism in psychiatry, geriatric medicine, nursing, and neurology.

Achievement of consensus

This study achieved consensus according to the criteria set out in the protocol. The required percent agreement for consensus was exceeded for the majority of treatments in the current treatment category and all treatments in all other categories. Items identified in round one were systematically removed to produce a final list of priority treatments for each category – current treatments (pharmacological and non-pharmacological were combined for overall BPSD as well as specifically for agitation and psychosis), future pharmacological treatments (overall, specific for agitation, and specific for psychosis), and future non-pharmacological treatments (overall, specific for agitation, and specific for psychosis).

Current treatments – overall and for agitation

Similar rankings were found for current treatments both for overall BPSD and specific to agitation, and thus, these symptoms were grouped together. The current treatments fell into three broad categories: (1) assessment of underlying causes, (2) non-pharmacological treatments, and (3) pharmacological treatments. Within these categories, eight treatments were prioritized. Highest priority was given to assessment of underlying causes. This was followed by a series of non-pharmacological approaches, specifically caregiver training, adaptation of the environment, person-centered care, and tailored activities. The final three treatment approaches were pharmacological, specifically citalopram, followed by analgesia and finally the antipsychotic risperidone. These are presented in order of priority in Table 2.

Future non-pharmacological treatments

Future preferred non-pharmacological approaches were consistent across the three categories (overall BPSD, agitation, psychosis), and were further discussed together. In the first two rounds of the Delphi process, three non-drug approaches were highlighted. The DICE (Describe, Investigate, Create, and Evaluate) (Kales *et al*., 2014; Kales *et al*., 2015) intervention which provides a structured approach to assessment of underlying causes, care planning including pharmacologic and non-pharmacoloic strategies and ongoing monitoring was considered to be highest priority, followed by training and empowering caregivers, such as the STAR-C (Teri *et al*., 2005) caregiver training programme, and music therapy. In the third round, based on discussion of number of current trials and inclusion criteria to be considered future/experimental, it was determined that DICE

Table 2. Consensus on current treatments for overall BPSD and agitation

TREATMENT OF OVERALL BSPD WITHIN AND AGITATION*	% AGREEMENT ACROSS PANEL +/−1 RANK SCORE	RANK
Thorough assessment and management of underlying causes	100%	1
Caregiver problem –solving/information/education	91%	2
Environmental adaptation/approaches	70%	3
Person-centered care	70%	4
Tailored activity program	70%	5
Citalopram	81%	6
Treat pain – Paracetamol/Analgesia	81%	7
Risperidone	64%	8

*Rank order identical for BPSD overall and for agitation.

Table 3. Consensus on emerging and experimental non-pharmacological treatments for overall BPSD, agitation, and psychosis

FUTURE NON-PHARMACOLOGICAL TREATMENTS	% AGREEMENT ACROSS PANEL WITHIN +/−1 RANK SCORE	RANK
DICE	100%	1
Music therapy	100%	2

Table 4. Consensus on future pharmacological treatments for agitation

FUTURE PHARMACOLOGICAL TREATMENTS FOR AGITATION	% AGREEMENT ACROSS PANEL WITHIN +/−1 RANK SCORE	RANK
Dextromethorphan/quinidine	100%	1
Mirtazapine	60%	2
Prazosin	50%	3

was the preferred first line non-drug treatment followed by music therapy (Table 3).

Future pharmacological treatments for agitation

Consensus on future and experimental pharmacological treatments for agitation identified several approaches that are considered to hold particular promise. While the combination treatment of dextromethorphan/quinidine was unanimously decided as the top future treatment; mirtazipine, prazosin, and THC were also highlighted as additional potential candidates (Table 4).

Current and future treatments for psychosis

Consensus was achieved for both current as well as future pharmacological treatment of psychosis in people with AD. There was a clear difference in treatments recommended for first and second line management of psychosis, compared to those recommended for agitation. For current treatments, the panel prioritized a thorough assessment of underlying causes as a first-line treatment followed by the antipsychotic risperidone. A number of other approaches were mentioned in the earlier Delphi rounds, but achieved a much lower agreement amongst the panel and were not included in the final consensus, including alternative antipsychotics haloperidol and quetiapine and citalopram (Table 5). When considering emerging treatments for future management of psychosis there was a clear consensus that of the pharmacological compounds currently in trials the most promising first-line approach is pimavanserin, followed by citalopram. Other pharmacological treatments highlighted in discussion included galantamine, melatonin, prazosin, and dextromethorphan/quinidine (Table 6).

Discussion

This study reports on an international Delphi consensus study and provides clear guidance on the most appropriate current treatment approaches for BPSD in AD (overall BPSD symptoms as well as those specifically for agitation and psychosis) and the most promising emerging treatments for the future. The study has found good consensus

Table 5. Consensus on the current treatment of psychosis

	% AGREEMENT ACROSS PANEL WITHIN +/−1 RANK SCORE	RANK
Thorough assessment and management of underlying causes	100%	1
Risperidone	100%	2

Table 6. Consensus on emerging and experimental pharmacological treatments for psychosis

FUTURE PHARMACOLOGICAL TREATMENT FOR PSYCHOSIS	% AGREEMENT ACROSS PANEL WITHIN +/−1 RANK SCORE	RANK
Pimavanserin	100%	1
Citalopram	100%	2

in a dedicated expert panel and has highlighted several key guiding principles for management. The recommendations for BPSD overall/agitation and psychosis were clearly different, with an increased emphasis on non-pharmacological treatment approaches for BPSD overall/agitation. This distinction is not currently fully represented in existing clinical guidance.

The consensus outcomes show a clear preference for an escalating approach to the management of BPSD overall/agitation and psychosis, commencing with the identification of underlying causes of symptoms. This is consistent with the large body of literature describing common triggers and causes of both agitation and psychosis which can be directly addressed, for example through changes to the person's immediate environment or treatment of existing medical conditions (Ballard and Corbett, 2010; Kales, 2015). The recommendations then diverged for BPSD overall/agitation and psychosis.

Four different targeted non-pharmacological approaches – caregiver training, adaptation of the environment, person-centered care, and tailored activities – were prioritized for BPSD overall/agitation prior to considering a pharmacological approach, highlighting the importance, and value of non-drug approaches. This emphasis on non-drug approaches is supported by robust evidence from recently published large clinical trials that have shown significant benefit to agitation following structured non-drug approaches that focus on caregiver training, person-centeredness and promotion of pleasant activities (Fossey *et al*., 2006; Ballard *et al*., 2016). Interestingly, when considering pharmacological treatment, two agents – citalopram and analgesia – were both prioritized for use above antipsychotic medication. There is clinical trial evidence to support both citalopram and stepped analgesia as treatment approaches which confer improvement in agitation (Husebo *et al*., 2011; Husebo *et al*., 2014). The use of citalopram and analgesic agents as an alternative to atypical antipsychotics is not emphasized in current guidelines.

Approaches to manage psychosis were markedly different from those for BPSD overall/agitation, reflecting the specific evidence base for psychosis in dementia. There was a clear message that non-drug approaches (apart from a thorough investigation of underlying causes) are of lower priority and value in people with psychosis. This is consistent with studies that report benefit to overall BPSD and agitation, but not psychosis with psychosocial approaches. Following the assessment of underlying causes, the panel consensus prioritized the use of pharmacological options. There was a clear consensus that risperidone be used as a first-line pharmacological approach, with minimal agreement on the use of alternative antipsychotics such as quetiapine or haloperidol. This output of the consensus process highlights the fact that there is not a "one size fits all" approach for BPSD as a group of symptoms, and that there is a need for dedicated guidance for the specific management of psychosis as a separate syndrome from agitation to ensure that both non-pharmacological and drug treatments are used appropriately in the context of different symptoms.

There were a number of emerging candidates discussed for the future treatment of agitation and psychosis. This area of consensus also showed that differing approaches were highlighted for agitation in comparison to psychosis. Two tailored non-drug approaches, DICE and music therapy, were agreed as the most promising future treatments for agitation, with the consensus reflecting the perceived importance of person-centered non-pharmacological treatment approaches and

caregiver training by the panel. Of note, since completion of the consensus, a large trial of a person-centered training and psychosocial care programme (WHELD) has been published, with benefits in quality of life and agitation (Ballard *et al.*, 2016). By consensus, the most promising future pharmacological treatments for agitation were dextromethorphan/quinidine, with a mix of support for mirtazapine and prazosin, and a wider range of compounds also highlighted as potential candidates in discussion. We would like to highlight that given the insufficient current evidence of efficacy and safety of future pharmacologic treatments like dextromethorphan/quinidine for agitation (phase III trial is currently in progress), it is our view that these treatments should not yet be used as clinical therapies for BPSD. This diversity of potential treatments highlights the positive momentum in research into treatments for agitation, and provides an indication of the likely treatments for future use.

Regarding future treatments for psychosis, the greatest priority was placed on pimavanserin, which has shown good safety and efficacy in people with Parkinson's Disease Psychosis (Cummings *et al.*, 2014). Pimavanserin is now licensed for this use in the US and trials in AD are underway.

This study has provided a robust and clear set of priorities for current and future treatment of agitation and psychosis in AD. A clear consensus was reached according to the pre-defined criteria, and the modified protocol enabled a more detailed discussion to be completed in person. However, there are limitations. The recommendations by this panel specifically pertain to the BPSD of AD; for example, the recommendations for psychosis in Parkinson's disease dementia or Lewy Body Dementia would be different (e.g. risperidone would not be a first-line treatment). The panel was of modest size, not all disciplines treating BPSD or countries were represented. The de-anonymization of the expert panel may have led to imbalance in opinion within the expert panel. This phenomenon is acknowledged in the published Delphi consensus, and can arise when individual panel members are particularly vocal or overwhelming in their opinions. However, reports from the panel meeting do not suggest a bias or dominance of any particular individual, and the experts involved contributed equally, and with confidence, to the discussions. The adapted method appeared to encourage more detailed discussion and elucidation of complex issues within the field that would not have been possible with a traditional remote Delphi process.

The consensus provides some clear suggestions for potential refinement of current treatment criteria and some prioritization of emerging therapies.

Conflict of interest

None.

Description of author's roles

Writing the article: Kales, Miller, Lyketsos, and Ballard. Formulating the research question(s): Kales, Lyketsos, and Ballard. Designing the study: Kales, Lyketsos, and Ballard

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