

Treatment of behavioral and psychological symptoms of dementia: a systematic review

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Summary

BPSD (Behavioral and Psychological Symptoms in Dementia) affects virtually all patients with dementia. The aim of this review is to present information on epidemiology, consequences and evidence-based non-pharmacological and pharmacological treatment approaches. The review also covers recent literature derived from a systematic literature Medline search on BPSD. Results indicate that BPSD are major risk factors for an earlier placement of affected individuals in nursing homes and a potentially more severe course of dementia over time. Treatment of BPSD is complex and includes both strategies.

Key words: dementia, BPSD, treatment

Introduction

The term BPSD (Behavioral and Psychological Symptoms in Dementia) was proposed in 1994. The International Psychogeriatric Association (IPA) proposed and elaborated this concept [1], BPSD have been well documented among patients with several types of dementia, including Alzheimer's disease (AD), vascular dementia (VaD), Parkinson's disease with dementia (PDD), frontotemporal lobe degeneration (FTLD), and more recently mild cognitive impairment (MCI) [2–5]. BPSD include a variety of symptoms like agitation, depression, apathy, repetitive questioning, psychosis, aggression, sleep problems, wandering, and a variety of inappropriate behaviors. One or more of these symptoms will affect the vast majority of individuals with dementia over the course of their illness [6].

The majority of persons with dementia and BPSD are located in their homes and cared for by family members. BPSD are strongly associated with stress and depression in caregivers, as well as reduced income from employment and lower quality of life [6].

Aim

The aim of the review is to cover the prevalence, types, outcomes and treatment of behavioral and psychological symptoms of dementia. In particular, it details the evidence base for non-pharmacological and pharmacological treatments, as well as an approach to assessing behaviors and deriving treatment plans. For this purpose, systematic reviews and single studies (literature search via medline) from the last 15 years are included. Based on methodological quality and study design, strength of evidence was assessed according to the criteria of the Oxford Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group 2001; Table 1).

Table 1. Level of evidence (Oxford Centre of Evidence-Based Medicine, 2001)

Level of evidence	Therapy/Prevention/Etiology/Harm
1a	Systematic review (with homogeneity) of randomized-controlled trials (RCTs)
1b	Individual RCT (with narrow confidence interval)
1c	All or none (all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it)
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., < 80% follow-up)
2c	"Outcomes" research; ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Frequency and relevance of BPSD

Dementia of all types was estimated to affect 44 million people worldwide in 2013 [6]. The number of persons with dementia is expected to reach 76 million in 2030 and 135 million by 2050 worldwide [7]. More than 75% of people are cared for by family or friends at home [8]. The Cache County study found that the five-year BPSD prevalence (at least one symptom) was 97%, with the most common symptoms being apathy, depression, and anxiety [9]. Symptoms often co-occur (for example, depression

and anxiety; wandering and sleep problems), increasing their impact on the affected persons and caregivers even more. Thus, the number of people with dementia and related BPSD is significant [9]. A number of studies confirm that more than 90% of AD patients will experience at least one BPSD symptom at some point during the course of their illness [4, 10]. A community-based epidemiological study found that 61% of AD patients exhibited one or more BPSD in the past month and 61% of those with no baseline BPSD developed at least one symptom within 18 months [5, 11]. In a nursing home study, a baseline prevalence of 76%, a two-year prevalence of 82%, and an annual incidence of 64% was reported [7].

Types of behavioral and psychological symptoms of dementia

BPSD often occur in clusters or syndromes identified as psychosis (delusions and hallucinations), agitation, aggression, depression, anxiety, apathy, disinhibition (socially and sexually inappropriate behaviors, motor disturbance, night-time behaviors, appetite and eating problems (Table 2) [12–17]. Although these symptoms are seen almost universally in dementia, regardless of the underlying etiology, some types of dementia are associated with specific BPSD. For instance, depression is more common in vascular dementia and hallucinations are seen more often in Lewy body dementia than in Alzheimer’s disease. People with frontotemporal dementia more often have behaviors typical of disinhibition, wandering, socially inappropriate behaviors, and apathy [18–20].

Table 2. Type and severity-related frequencies of BPSD (behavioral and psychological symptoms of dementia)

Syndrome	Symptom	Frequency range (%)			Overall range (%)	High frequency according to the type of dementia
		Light	Moderate	Severe		
Psychosis						more common in ↑DLB > ALZ-D
	Hallucinations	15	36	82	17–24	
	Delusions	58	72	47	33–40	
Depression		62	60	37	54–64	more common in vascular dementia and early ALZ-D↑
	Anxiety	69	66	58	22–35	
Apathy					33–63	all forms of dementia, FTLD↑
	Social withdrawal				21–88	
Aggression		54	66	66	24–34	

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	Resistance				27–65	
	Verbal				11–61	FTLD↑
	Physical				0–46	FTLD↑
Agitation		73	94	?	38–64	
	Walking Aimlessly				0–50	
	Pacing				26–48	
	Restlessness				22–27	
	Sleep problems	35	55	40	0–47	

modified [22, 103, 126]; DLB – Lewy Body dementia; ALZ-D – Alzheimer’s Dementia; FTLTLD – Frontotemporal lobe dementia

Pertaining dementia severity (light, moderate, severe), BPSD occur across all stages, although their type and prominence may vary over time. For example, anxiety and depression are common in early stage Alzheimer’s disease and may worsen with progression. Agitation (a broad category that includes excessive psychomotor activity such as pacing, trailing, restlessness, dressing and undressing, and emotional distress) may increase with disease severity [8, 13, 21, 23]. During the course of dementia, apathy is commonly reported by family members across all stages of dementia and tends to worsen over time. In comparison delusions, hallucinations, and aggression are often episodic and more common in moderate to severe stages of the disease [6].

Outcomes of behavioral and psychological symptoms of dementia

Although cognitive symptoms and loss of memory are the main characteristics of dementia, behavioral and psychological symptoms often dominate both the presentation and course of disease [24–28]. Thus, BPSD often create the most difficulties for people with dementia, their caregivers and providers. Unlike cognitive and functional deficits, for which there is a downward trajectory of decline, these symptoms tend to fluctuate episodically over time and may last for at least six months. Their episodic nature contributes to the complexity of their prevention and treatment [6].

BPSD often lead to significantly earlier placement in a nursing home [26, 28], as well as excess morbidity, mortality, and hospital admissions [27]. Approximately one third of dementia care costs have been attributed to the management of BPSD owing to greater use of health services, direct care costs, and family time spent in daily oversight [29, 30]. Although patients in the Cache County study with untreated BPSD may have a faster disease progression than those without such symptoms, it is not yet clear whether treating these symptoms slows dementia decline [15].

BPSD are also associated with poor caregiver outcomes, including reduced quality of life, worse health, and reduced income from employment [31–33]. Caregivers manag-

ing such symptoms are more distressed or depressed (or both) than those caregivers of people with dementia alone or with other chronic diseases [34]. Managing wandering, repetitive vocalizations, sleep disturbances, and other symptoms such as resisting or refusing care and restlessness are among the most problematic and distressing aspects of care provision [35, 36].

Treatment approaches introduction

BPSD have a complex etiology. Thus one single treatment approach does not exist due to the variety of symptoms (Table 1). Furthermore, management involves thinking beyond patient-centered care and considering the special role and training of family members, nurses and other caregivers.

Table 3. Review of studies on treatment of behavioral and psychological symptoms in dementia (BPSD)

First Author	Year	Goal of treatment	Intervention	Degree of evidence	Details
Brody [50]	2012	Meta-analysis of 23 included unique randomized or pseudorandomized non-pharmacological interventions with family caregivers and frequency or severity of BPSD	Non-pharmacological	1a	Non-pharmacological interventions were effective in reducing behavioral and psychological symptoms, with an overall effect size of 0.34
O'Neil [43]	2011	Non-pharmacological interventions for behavioral symptoms in dementia	Non-pharmacological	2a	Lack of Evidence of most non-pharmacological interventions, further research needed
Thuné-Boyle [112]	2012	"Qualitative review": effect of exercise on behavioral and psychological symptoms of dementia	Non-pharmacological	5	Exercise appears to be beneficial in reducing some BPSD, especially depressed mood and agitation and may also improve sleep and reduce "wandering"
Cohen-Mansfield [39]	2013	Physician's practice and familiarity with treatment for agitation	Non-pharmacological	4	Psychotropic medications are the treatment of choice among nursing home physicians in Israel
Kales [6]	2015	Assessment and management of behavioral and psychological symptoms	Non-pharmacological	3a	Drug treatment is more effective than non-pharmacological interventions
Mixed pharmacological and non-pharmacological approaches					

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Tampi [111]	2011	Systematic review on treatment of BPSD	Pharmacological and non-pharmacological treatments	3a	Effective treatment strategies for BPSD include various non-pharmacological and pharmacological approaches. The treatment of these behaviors should ideally start with non-pharmacological approaches, with pharmacotherapy reserved for behaviors that are severe, persistent, and resistant to non-pharmacological treatments
Pharmacological approaches: Antipsychotics					
Schneider [113]	1990	Meta-analysis of controlled trials of neuroleptic treatment in dementia	Antipsychotics	1a	This indicates that 18 of 100 dementia patients benefited from neuroleptic treatment
Lonergan [54]	2002	Haloperidol for agitation in dementia	Antipsychotics	1a	The present study confirmed that haloperidol should not be used routinely to treat patients with agitated dementia
Pollock [83]	2002	Comparison of citalopram, perphenazine and placebo on agitation in Alzheimer's disease	Antipsychotics	2a	Citalopram was found to be more efficacious than placebo in the short-term hospital treatment of psychotic symptoms and behavioral disturbances in non-depressed, demented patients
Schneider [30]	2005	Meta-analysis, risk of death with atypical antipsychotic treatment in dementia; 15 studies with 16 contrasts of antipsychotic drugs with placebo, and involving a total of 5,387 patients, were included in the review	Antipsychotics	1a	The pooled OR of death for all 15 trials was 1.54 (95% confidence interval, CI: 1.06, 2.23, $p = 0.02$) in favor of placebo, with no significant heterogeneity among the studies
Sink [88]	2005	Pharmacological treatment of neuropsychiatric symptoms in dementia	Antipsychotics	2a	It is unclear whether the benefits outweigh the adverse effects of this agent

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Ballard [114]	2006	Olanzapine for agitation and aggression but not for psychosis	Antipsychotics	2a	Olanzapine was also found to be efficacious for agitation and aggression
Schneider [60]	2006	42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo	Antipsychotics	1a	No significant differences were noted among the groups with regard to improvement on the Global Clinical Impression Scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo ($p = 0.22$)
Schneider [56]	2006	15 trials including 16 contrasts of atypical antipsychotics with placebo met selection criteria: aripiprazole ($k = 3$), olanzapine ($k = 5$), quetiapine ($k = 3$), and risperidone ($k = 5$). A total of 3,353 patients were randomized to drug and 1,757 to placebo.	Antipsychotics	1a	Small statistical effect sizes on symptom rating scales support the evidence for the efficacy of aripiprazole and risperidone. Incomplete reporting restricts estimates of response rates and clinical significance
Gill [115]	2007	Mortality using conventional antipsychotics vs. atypical	Antipsychotics/ Adverse events	1a	Increased risk of mortality in older adults using conventional versus atypical antipsychotics
Katz [116]	2007	Risperidone in treatment of Alzheimer's disease	Antipsychotics	2a	The efficacy of risperidone appeared to be higher in patients with more severe psychotic symptoms
Schneeweiss [113]	2007	Mortality using conventional antipsychotics vs. atypical	Antipsychotics/ Adverse events	1a	Increased risk of mortality in older adults using conventional versus atypical antipsychotics
Yury and Fisher [61]	2007	Effectiveness of atypical antipsychotics in treatment of behavioral problems in persons with dementia	Antipsychotics	1a	The overall effect size vs. placebo for "atypical" antipsychotics 0.31 (95% CI = 0.08–0.54)

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Douglas [64]	2008	Exposure to antipsychotics and risk of stroke	Antipsychotics/ Adverse events	4	The risk may be even higher than that with conventional antipsychotics
Sultzer [62]	2008	Clinical symptom response to atypical antipsychotic medication	Antipsychotics	1a	A subsequent analysis of CATIE-AD data indicated that atypical antipsychotics may be more effective for particular symptoms such as anger, aggression, and paranoid ideas
Ballard [63]	2010	Aripiprazole and Risperidone	Antipsychotics	3a	In conclusion, it is important in most situations to limit the use of antipsychotic medication to short-term treatment
Devanand [74]	2012	Depressed mood and incidence of Alzheimer's disease	Antipsychotics/ Adverse events	2b	Discontinuation of the antipsychotic was associated with an increased risk of relapse
Kales [53]	2012	Risk of mortality, antipsychotics in patients with dementia	Antipsychotics/ Adverse events	2b	Mortality was highest in those receiving haloperidol (relative risk 1.54, 95% CI 1.38 to 1.73), followed by risperidone (reference, relative risk 1) and olanzapine (0.99, 95% CI 0.89 to 1.10), then valproic acid (0.91, 95% CI 0.78 to 1.06), and lastly quetiapine (0.73, 95% CI 0.67 to 0.80)
Declercq [75]	2013	Withdrawal vs. continuation of chronic antipsychotic drug for older people with dementia	Antipsychotics/ Adverse events	1a	Discontinuation of the antipsychotic was associated with an increased risk of relapse
Kales [6]	2015	Conventional antipsychotic agents	Antipsychotics	2a	No clear evidence for efficacy of conventional antipsychotic
Kales [6]	2015	Assessment and management of behavioral and psychological symptoms	Antipsychotics	3a	Olanzapine was also found to be efficacious for agitation and aggression
Kales [6]	2015	Mortality drug vs. Placebo	Antipsychotics/ Adverse events	2a	Although limited data suggest that conventional antipsychotics may be associated with an increased risk of stroke, the risk is more established with atypical antipsychotics

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Tan [59]	2015	Significant efficacy of atypical antipsychotics on psychiatric symptoms and cognitive functions	Antipsychotics	1a	This meta-analysis demonstrated a significant efficacy of atypical antipsychotics on psychiatric symptoms and cognitive functions compared to placebo
Pharmacological approaches: Antidepressants					
Bains [76]	2002	Antidepressant for treating depression in dementia	Antidepressants/ SSRI	1a	Selective serotonin reuptake inhibitors (SSRIs) had good tolerability and a favorable treatment response
Kirby [85]	2002	Hyponatremia in elderly patients treated with SSRI and Venlafaxine	Antidepressants/ Adverse events	2b	SSRIs, adverse events do occur
Pollock [55]	2002	Comparison of perphenazine, citalopram and placebo for treatment in demented patients	Antidepressants	2b	Only the citalopram trial showed any benefit
Lyketsos [77]	2003	Sertraline therapy for treatment of depression in dementia	Antidepressants/ SSRI	1b	Good treatment response to sertraline
Sink [88]	2005	Meta-analysis of pharmacological treatment of neuropsychiatric symptoms of dementia; 25 RCTs and 4 meta-analyses were included in the review	Antidepressants, Antipsychotics and other compounds	2a	This review concluded that of the drugs used for treating neuropsychiatric symptoms of dementia, risperidone and olanzapine had the best evidence for efficacy although their effect sizes were modest and they increased the risk of stroke. However, there was only a small evidence base for most of the drugs considered in the review.
Henry [84]	2011	Antidepressants in treatment of dementia	Antidepressants	2a	Eight trials using an SSRI compound and three trials using trazodone showed benefit in the treatment of BPSD
Seitz [81]	2011	Antidepressants for agitation and psychosis in dementia	Antidepressants	1a	Study found evidence for a reduction in agitation with sertraline and citalopram compared with placebo

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Sepehry [69]	2012	Effect of SSRI on depression in Alzheimer's disease	Antidepressants/SSRI	1a	SSRIs reported a lack of clear benefit for depression
Zivin [87]	2013	Citalopram at doses exceeding 40mg	Antidepressants/Adverse events	1b	No increased risk of ventricular arrhythmia or cardiac mortality with citalopram or sertraline
Drye [86]	2014	Changes in QTc interval in treatment with citalopram for agitation	Antidepressants/Adverse events	1b	Only a small number of patients in this study met the gender specific threshold of QT prolongation
Porsteinsson [82]	2014	Effect of citalopram on agitation in Alzheimer's disease	Antidepressants	1b	Citalopram treatment showed significant improvement over placebo
Porsteinsson [82]	2014	Worsening of cognition and QT prolongation in the citalopram group	Antidepressants/Adverse events	1b	Worsening of cognition and QT prolongation were seen in the citalopram group
Kales [6]	2015	Mortality drugs vs. placebo	Antidepressants/Adverse events	2b	No increased risk of ventricular arrhythmia or cardiac mortality with citalopram or sertraline
Pharmacological approaches: Anticonvulsants/Mood stabilizers					
Tariot [94]	1998	Carbamazepine for treatment of agitation in dementia	Anticonvulsants	2a	Symptoms decreased significantly in the carbamazepine vs. control group
Olin [96]	2001	Carbamazepine in Alzheimer's disease	Anticonvulsants	2a	Modest clinical benefit in carbamazepine treatment
Miller [109]	2001	Gabapentin for treatment of dementia	Gabapentin	4	No difference between gabapentin and placebo
Lonergan [92]	2009	Valproic acid for agitation in dementia	Anticonvulsants	1a	Valproate not helpful for agitation
Sink [88]	2005	Pharmacological treatment of neuropsychiatric symptoms of dementia; studies on mood stabilizers (carbamazepine, divalproex sodium, sodium valproate) were included	Anticonvulsants	2a	Mood stabilizers; 5 RCTs (342 participants); Three RCTs found that valproate was ineffective for treating neuropsychiatric symptoms and that it also caused adverse events. Carbamazepine was beneficial in one trial and ineffective in another.

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Konovalov [93]	2008	Anticonvulsants for treatment of behavioral and psychological symptoms in dementia	Anticonvulsants	2a	Low-dose sodium valproate is ineffective in the treatment of agitation in persons with dementia; high-dose divalproex sodium is associated with an unacceptable rate of adverse effects
Pharmacological approaches – Cholinesterase inhibitors/Memantine					
Mc Keith [100]	2000	Rivastigmine and dementia with Lewy bodies	Cholinesterase inhibitors	1b	No difference between rivastigmine and placebo
Olin [98]	2002	Depression in Alzheimer's disease	Cholinesterase inhibitors	1a	Benefit of cholinesterase inhibitors
Trinh [47]	2003	Cholinesterase inhibitors in treatment of neuropsychiatric symptoms	Cholinesterase inhibitors	2a	Benefit of cholinesterase inhibitors
Courtney [99]	2004	Donepezil treatment in patients with Alzheimer's disease	Cholinesterase inhibitors	1b	No benefit for donepezil
Loy [117]	2004	Galantamine for Alzheimer's disease	Cholinesterase inhibitors	1a	Benefit of cholinesterase inhibitors
Mc Shane [103]	2006	Memantine for dementia	Memantine	1a	Benefit of memantine
Howard [118]	2007	Donepezil for the treatment of agitation	Cholinesterase inhibitors	1b	No benefit for donepezil
Gauthier [21]	2008	Improvement by memantine	Memantine	2a	Benefit of memantine
Wilcock [67]	2008	Memantine for agitation, aggression and psychosis	Memantine	2a	Benefit of memantine
Dubois [101]	2012	Donepezil in Parkinson's dementia	Cholinesterase inhibitors	1b	No difference between donepezil and placebo
Fox [104]	2012	Memantine for agitation in Alzheimer's disease	Memantine	1b	No benefit over placebo
Rolinski [102]	2012	Cholinesterase inhibitors in Lewy Body dementia (DLB), Dementia in Parkinson's disease (PDD)	Cholinesterase inhibitors	1a	The currently available evidence supports the use of cholinesterase inhibitors in patients with PDD, with a positive impact on global assessment, cognitive function, behavioral disturbance and activities of daily living rating scales. The effect in DLB remains unclear

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Dols [97]	2013	The prevalence and management of side effects of lithium and anticonvulsants	Cholinesterase inhibitors	2a	Small effects of cholinesterase inhibitors
Pharmacological approaches – Sedatives/Hypnotics					
Meehan [108]	2002	Comparison of olanzapine, lorazepam and placebo	Lorazepam	2b	Short time effects of lorazepam
Peisah [110]	2011	Benzodiazepines	Benzodiazepines	4	Many side effects of benzodiazepines in elder people
Non-pharmacological approaches					
Teri and Logsdon [119]	1991	Pleasant activities for Alzheimer's disease patients	Non-pharmacological	4	Pleasant events schedule, activities are identified, no empirical data
Gitlin [120]	2001	Meta-analysis 9 active compared with 6 control conditions of the Resources for Enhancing Alzheimer's Caregiver Health (REACH) project	Non-pharmacological	2a	For depressive symptoms, a statistically significant association of group assignment was found for Miami's family therapy and computer technology intervention
Gitlin [52]	2001b	5x90-min home visits by occupational therapists vs. usual care	Non-pharmacological	2b	The environmental program appears to have a modest effect on dementia patients' IADL dependence
Gitlin [51]	2003	Are environmental interventions effective on Alzheimer's disease	Non-pharmacological	3a	The primary conclusion is that although 90% of the 63 reviewed studies reported positive outcomes, most studies were methodologically flawed, involved small samples, and were conducted in nursing homes
Ouslander [83]	2003	Management of depression and behavioral symptoms associated with dementia	Non-pharmacological	2a	Systematic review with recommendations on the use of non-pharmacological treatments in BPSD
Teri [121]	2003	Exercise plus behavioral management in patients with Alzheimer's disease vs. routine medical care	Non-pharmacological	1a	Exercise training combined with teaching caregivers behavioral management techniques improved physical health and depression in patients with Alzheimer's disease

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Cohen-Mansfield [40]	2005	Non-pharmacological intervention for persons with dementia	Non-pharmacological	3b	Non-pharmacological interventions have beneficial effects
Gitlin [48]	2008	Tailored programs Training for caregivers vs. waiting list	Non-pharmacological	2b	Tailored programs training for caregivers reduced BPSD
Hansen [122]	2006	Massage and touch for dementia, Cochrane review on 34 studies	Non-pharmacological	1a	Massage and touch may serve as alternates or complements to other therapies for the management of behavioral, emotional and perhaps other conditions associated with dementia. More research is needed, however, to provide definitive evidence about the benefits of these interventions
Kong [123]	2009	Non-pharmacological intervention for agitation in dementia	Non-pharmacological	2b	Systematic review and meta-analysis, sensory interventions were the only type of non-pharmacological intervention in dementia that showed beneficial effects in reducing agitation
O'Connor [42]	2009	Psychosocial treatment of behavior symptoms in dementia	Non-pharmacological	2b	There was some evidence from a small number of studies that care people education, music, physical exercise, recreation and validation therapy were more effective in reducing BPSD compared with attention controls
Gitlin [124]	2010	Home-based intervention with dementia COPE vs. control	Non-pharmacological	1b	Among community-living dyads, a non-pharmacologic bio-behavioral environmental intervention compared with control resulted in better outcomes for COPE dyads at 4 months. Although no group differences were observed at 9 months for patients, COPE caregivers perceived greater benefits.

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In the following sections, current evidence for non-pharmacological and pharmacological treatments is presented.

Available non-pharmacological treatments

Non-pharmacological treatments include a vast variety of behavioral, environmental and caregiver supportive interventions. Numerous guidelines, medical organizations, and expert groups recommend non-pharmacological strategies as the preferred first-line treatment approach with the exception of emergency situations [37]. However, these strategies have largely not been translated into current clinical management and standard care [38]. Further, drugs are preferred over non-pharmacological strategies for several reasons: lack of provider training in the use of non-pharmacological strategies [39], time needed, lack of staff and equipment for such approaches. Moreover, lack of clear guidelines on dosing and timing of these strategies regarding type and severity of dementia and BPSD are often worsening the treatment context. The perceived lack of efficacy from studies compared to pharmacological treatments often leads to a preference of drug treatment strategies by clinicians [6] (LoE 3a). Concerns about efficacy may be secondary to the heterogeneity of behavioral interventions encompassing everything from aromatherapy and massage to supportive and psycho-educational interventions for caregivers. Providers often have to get acquainted with these approaches, in particular their efficacy, choice and implementation. Previous studies reported lack of efficacy of several approaches due to small sample sizes, lack of methodological rigor, focus on patients with more severe dementia and those living in residential settings [40] (LoE 3b), [41] (LoE 2b), [42] (LoE 2b).

However, several widely suggested and employed approaches lack evidence (positive or negative) from studies. These include acupuncture, aromatherapy (use of fragrant plant oils), cognitive or memory training, reminiscence therapy (discussion of past experiences), light therapy, simulated presence therapy (use of audiotaped recordings of family members' voices), Snoezelen (placing the person with dementia in a soothing and stimulating environment known as a "Snoezelen Room") and validation therapy (working through unresolved conflicts) [6] (LoE 3a).

Treatment of specific BPSD with non-pharmacological interventions

Several intervention studies for specific behaviors (such as wandering and agitation) are even more limited than the studies looking at behavioral and psychological symptoms of dementia in general. Four systematic reviews of non-pharmacologic strategies found no evidence of benefit for physical activity or walking programs for wandering in randomized trials [43] (LoE 2a). Several randomized trials have found that engagement in physical activity and pleasant events reduced depression in persons with dementia living at home [44] (LoE 4), [45] (LoE 1a). A recent systematic review found that exercise had no impact on mood [46] (LoE 3b), although it may improve

night-time sleep [47] (LoE 5). There is some evidence from a few randomized controlled trials (RCTs) that specific symptoms of aggression, agitation, and wandering were reduced with use of music therapy. Although these results are promising, more high quality RCTs on these approaches are needed [6] (LoE 2a). Strategies such as distraction, backing away, and leaving the room have been reported to be helpful for symptoms of aggression, but, again, more research is needed. There is some evidence (based on two RCTs) that hand massage reduces agitation in the short term and that touch can encourage eating, but more RCTs are needed.

Interventions for family caregivers

In this type of approach, problem solving with a family caregiver to identify potential precipitating and modifiable causes of BPSD is followed by efforts to modify these causes with selected non-pharmacological strategies. Two studies in VA (Veterans Affairs) BPSD populations incorporated good dementia care and support programs for caregivers and also integrated a tailored problem-solving approach for working with caregivers with regard to behaviors [47, 48]. Both trials showed significant reductions in BPSD frequency.

Another “Tailored Activity Program (TAP)” used eight sessions with occupational therapists to train caregivers in customized activity based on the person with dementia’s current and previous interests, cognitive and physical abilities [49] (LoE 2b). It showed significant reductions at four months in the frequency of problem behaviors ($p = 0.14$; Cohen’s $d = 0.75$) [35] (LoE 1b) and caregivers’ appraisal of time they are “on duty” ($p = 0.001$; Cohen’s $d = 0.74$). Similarly, the COPE (Care of Persons with Dementia in their Environments) study involved up to 12 contacts by health professionals to assess underlying medical problems and train caregivers to identify care recipients’ strengths and weaknesses to problem solve interventions [35] (LoE 1b). Results at four months included significant improvements in patients’ functional dependence (adjusted mean difference 0.24; 95% CI 0.03–0.44) and wellbeing of caregivers (adjusted mean difference 0.22; 95% CI 0.08–0.36).

The ACT (Advancing Caregiver Training) study used 11 visits by health professionals working with caregivers to identify potential triggers of problem behaviors (including underlying medical causes) and train caregivers to modify them [35] (LoE 1b). At four-month follow-up, improvement in target behaviors was significantly greater in the intervention group (67.5% vs. 45.8%, $p = 0.002$). The study also reported significant reductions in caregivers’ mental problems (adjusted mean difference -0.93 , -1.76 to -0.10) and negative communications with the demented individuals (-0.93 , 0.22; 95% CI -1.69 to -0.17), as well as enhanced caregivers’ confidence in managing BPSD (0.33, 0.22; 95% CI 0.08 to 0.5). Similar outcomes were found at 24 weeks, as well as a significant difference between the intervention and controls in improved ability to cope with BPSD patients at home (46.4% vs. 17.6%, $p = 0.001$).

A meta-analysis of 23 randomized clinical trials, involving almost 3,300 community dwelling patients, looked at interventions aimed at family caregivers [50] (LoE 1a). It confirmed that such interventions significantly reduced behavioral symptoms (effect size 0.34, 95% CI 0.20 to 0.48 [6]. Although the effect size was small, it is greater than that found in trials of antipsychotics for behavioral symptoms, as well as cholinesterase inhibitors for memory symptoms [50].

Environmental approaches

These include recognizing factors in the afflicted person's environment [6]:

- Over-stimulation (for example, excess noise, people, or clutter in the home) or under-stimulation (for example, lack of anything of interest to look at);
- Safety problems (for example, access to household chemicals or sharp objects or easy ability to exit the home);
- Lack of activity and structure (for example, no regular exercise or activities that match interests and capabilities);
- Lack of established routines (for example, frequent changes in the time, location, or sequence of daily activities).

A qualitative review of 63 research studies on the effects of environmental interventions provided evidence for its role in preventing and reducing behavioral symptoms, such as wandering or agitation [51] (LoE 3a). Although 90% of the studies included into the review presented positive effects, most studies did not use randomized designs. Of 11 studies, six were conducted in long-term care, two in dementia special care units, two in home environments, and one in different settings. All but one reported improvements in a wide range of outcomes, including behavioral symptoms, overall wellbeing, activity engagement, wandering (attempting to leave the facility, nursing home or living residence), and acceptance of care.

A wide range of environmental strategies have been tested, including reduction of clutter, use of color contrasts and signs. Two RCTs which included training families in the use of these strategies at home also had positive outcomes [49, 52] (LoE 2b). Because these strategies are often used in combination it is difficult to pinpoint one preferred approach; rather, a combination of adjustments to the environment seems to yield behavioral changes.

Known potential adverse events

Although non-pharmacological strategies do not carry the level of risk associated with drugs, the potential for adverse effects should not be ignored. Several studies have reported increased agitation with cognitive or emotion-oriented interventions, and increased agitation and physical aggression have also been reported for sensory

approaches such as music therapy, massage or touch therapies, and aromatherapy [43] (LoE 2a).

Summary of non-pharmacological treatments

The non-pharmacological approaches with the strongest evidence base are those based on family caregiver interventions, which have been shown to have even greater effect than antipsychotics [50] (LoE 1a). These approaches typically provide the caregiver with education and support, training in stress reduction or cognitive reframing techniques (or both), and specific skills in problem-solving to manage BPSD. They include increasing activity enhancing communication; reducing the complexity of the physical environment; and simplifying tasks for the individual with BPSD. Individual non-pharmacological approaches (such as music and physical activity) may be used within such approaches as tailored activities [6] (LoE 2a).

Drug treatment strategies (pharmacotherapy)

In the USA, no compound has been approved by the FDA for behavioral and psychological symptoms of dementia, thus all drugs are used off-label. In Canada, risperidone is approved for symptomatic management of behavior in severe dementia.

Current treatment strategies for BPSD include various pharmacological (e.g., antipsychotics, antidepressants, mood stabilizers, cognitive enhancers) approaches [52] (LoE 3a). Pharmacotherapy should be initiated only if the patient's symptoms have not responded adequately to non-pharmacological interventions, if there is no underlying medical condition causing these symptoms, and if these symptoms are not related to a medication effect. Although these non-pharmacological and pharmacological treatments are effective in decreasing the burden of BPSD, they usually require sustained input from a multidisciplinary team and ongoing staff training to maintain superior quality of care for patients with BPSD [50] (LoE 3a).

Antipsychotics

A systematic review of two meta-analyses (12 RCTs) and two additional RCTs found no clear evidence for efficacy of conventional antipsychotic agents on several BPSD [53] (LoE 2a). However, study sample sizes were often small and follow-up was for a maximum of 12 weeks in most trials. Haloperidol may have a slight benefit for aggression (at doses of 1.2–3.5mg/d; effect size – 0.31, 95% CI – 0.49 to – 0.13), but it is unclear whether the benefits outweighs the adverse effects of this agent (including extrapyramidal symptoms and sedation) [6, 54] (LoE 1a), [55] (LoE 2a), [30] (LoE 1a), [56, 57] (LoE 2a).

There have been at least 15 RCTs of atypical antipsychotics for BPSD, but several of these are not published. Taken together, more than 5,000 patients were involved and

treated for 8–12 weeks in general. A meta-analysis found evidence for symptomatic efficacy of aripiprazole (three trials; standardized mean difference (SMD) = -0.22 ; -0.36 – 0.08 ; $Z = 3.08$; $p = 0.002$) and risperidone (five trials; SMD -0.18 ; $Z = 3.43$; $p = 0.0006$) but not olanzapine (five trials) [6] (LoE 1a).

There was insufficient evidence for quetiapine because the three trials with this antipsychotic used different selection criteria and outcomes and could not be statistically combined. Most of the aripiprazole and risperidone trials were conducted in nursing home patients. There was evidence that less severe cognitive impairment, the presence of psychosis, and being an outpatient were each associated with lower efficacy. A second meta-analysis found similar results with the exception that olanzapine was also found to be efficacious for agitation and aggression (dose 5–10mg: weighted mean difference -0.77 ; -1.44 to -0.10 ; $p = 0.03$ [6]), but not psychosis [58] (LoE 2a). In a recent review and meta-analysis [59] (LoE 1a), 23 relevant RCTs with 5,819 participants were identified. This meta-analysis demonstrated a significant efficacy of atypical antipsychotics on psychiatric symptoms and cognitive functions compared to placebo. In the meta-analysis, the weighted mean differences (WMDs) in change scores for psychiatric symptoms were in favor of aripiprazole (-4.4 , 95% CI -7.04 to -1.77) and risperidone (-1.48 , 95% CI -2.35 to -0.61) compared to placebo. In cognitive effects, WMDs in change scores for the Clinical Global Impression-Change were in favor of aripiprazole, risperidone, olanzapine and quetiapine which ranged from -0.30 points mean difference (95% CI -0.59 to -0.01) in the aripiprazole trials to -0.43 (95% CI -0.62 to -0.25) in the risperidone group. Patients receiving atypical antipsychotics showed no difference in risk for injuries or falls ($p > 0.05$), significantly higher risks ($P < 0.05$) for somnolence, urinary tract infection, edema and abnormal gait. However, there was no significant increased rate of lethal outcomes (OR 1.06 (95% CI 0.65 to 1.73; $Z = 0.24$, $p = 0.81$)). The risk did not differ across investigated antipsychotics.

The efficacy of risperidone appeared to be higher in patients with more severe psychotic symptoms (effect size 0.29; 0.12 to 0.469) [60] (LoE 2a). Taken together, the overall effect size vs. placebo for “atypical” antipsychotics ranged from 0.16 ($Z = 3.89$; $p = 0.0001$) in one meta-analysis [60] (LoE 1a) to 0.31 (95% CI = 0.08–0.54) in another [61] (LoE 1a). The latter meta-analysis, covering studies between 1999 and 2006, included 13 studies which treated 1,015 subjects with antipsychotics and 6,688 with placebo. Medications studied were risperidone, olanzapine, and quetiapine. Other studies examined other types of medications, such as typical versus atypical antipsychotics, but only data for atypical antipsychotics were included in the meta-analysis. The mean effect size for 7 placebo-controlled studies was 0.45 (95% CI 0.16–0.74) for atypical antipsychotics, and 0.32 (95% CI 0.10–0.53) for placebo.

Another study (The Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer’s Disease – CATIE-AD) was a 42-site, double-blind, placebo-controlled

trial of 421 subjects with BPSD. The targeted syndromes included psychosis, aggression or agitation. The follow-up period was up to 36 weeks and the main outcome was time to discontinuation [30] (LoE 1a). No significant differences were found across groups in overall time to discontinuation or in clinical improvement. However, time to discontinuation for lack of efficacy favored risperidone (odds ratio 0.61, 0.41 to 0.89; $p = 0.01$) and olanzapine (0.51; 0.35 to 0.27; $p > 0.0001$) over placebo, whereas time to discontinuation for adverse events favored placebo over drug treatments (olanzapine: hazard ratio 4.32, 1.84 to 10.12; $p < 0.001$; risperidone: HR 3.62, 1.45 to 0.04; $p = 0.006$). In the group of patients who received quetiapine, time to discontinuation for lack of efficacy was not different from that in the placebo group, and time to discontinuation for adverse events favored placebo (quetiapine: hazard ratio: 3.58, 1.44 to 8.91; $p = 0.006$). A subsequent analysis of CATIE-AD data indicated that atypical antipsychotics may be more effective for particular symptoms such as anger, aggression, and paranoid ideas [62] (LoE 1a).

Adverse events with antipsychotics

Adverse events associated with typical antipsychotics include all of those associated with atypical agents (below) as well as a greater risk of anticholinergic effects, delirium, hyperprolactinemia, postural hypotension, prolonged QT, sexual dysfunction, and extrapyramidal symptoms (including parkinsonism, dystonia and tardive dyskinesia) [30] (LoE 1a). Atypical antipsychotics are associated with weight gain, diabetes, and the metabolic syndrome [56], cognitive worsening; seizures and delirium (clozapine); somnolence (clozapine, olanzapine, and quetiapine); extrapyramidal symptoms (risperidone); and abnormal gait (risperidone and olanzapine) [63] (LoE2a), [30] (LoE 1a). Although limited data suggest that conventional antipsychotics may be associated with an increased risk of stroke, the risk is more established with atypical antipsychotics [6, 64] (LoE 4). Pooled data from risperidone trials indicate that it is associated with a three-fold increased risk of cerebrovascular events, which maybe a class effect for all antipsychotics (a meta-analysis showed that stroke occurred in 1.9% of the drug group versus 0.9% of the placebo group, with an odds ratio of 2.13, 1.20 to 3.75; $Z = 2.60$; $p = 0.009$) [63] (LoE2a), [30] (LoE 1a). Finally, patients with Lewy body dementia are at increased risk of having adverse effects with antipsychotics and the effects are worse than in other patients with dementia, so extra caution should be used if prescribing these drugs for these patients. As a consequence, the FDA announced in 2005 that atypical antipsychotics were associated with a 1.7-fold increase in mortality compared with placebo (FDA 2005). The report was based on a re-analysis of 17 placebo-controlled trials (several of which were unpublished at this time). A black box warning for the use of atypical antipsychotics for BPSD was announced. A meta-analysis found an odds ratio for mortality with these drugs of 1.54 (1.06 to 2.23; $Z = 2.28$, $p = 0.02$), with pooled events of 3.5% mortality for the drug

versus 2.3% for placebo [6] (LoE 2a). In 2004, the European Agency for the Evaluation of Medicinal Products (now known as the European Medicines Agency) also issued public advice about the increased risk of cerebrovascular adverse events and mortality in elderly patients with dementia receiving olanzapine (EMA, 2011).

A similar black box warning for conventional antipsychotics, based on two observational studies that showed increased risk of mortality in older adults using conventional versus atypical antipsychotics, was announced in 2007 [65] (LoE 1a), [66] (LoE 1a). Conventional antipsychotic use was associated with an even greater risk of death than that observed with atypical antipsychotic use, and this risk was evident at 30 days (community-dwelling cohort: adjusted HR 1.55; 95% CI 1.19–2.02; adjusted risk difference 1.1 percentage points; long-term care cohort: adjusted HR 1.26; 95% CI 1.04–1.53; adjusted risk difference 1.1 percentage points, respectively). The increased mortality risk associated with conventional antipsychotic use versus atypical antipsychotic use and new atypical antipsychotic use versus non-use persisted to 180 days in both patient populations (community-dwelling cohort: adjusted HR 1.23). Another meta-analysis used combined data from two RCTs (risperidone-placebo and quetiapine-placebo) that had haloperidol arms (243 patients received haloperidol and 239 received placebo). It found 15 deaths (6.2%) with haloperidol and nine (3.78%) with placebo, resulting in an odds ratio of 1.68 (95% CI 0.72 to 3.92; $p = 0.23$) [30] (LoE 1a).

Subsequent observational studies have confirmed concerns about increased mortality in patients with dementia with conventional antipsychotics versus atypical antipsychotics [67], and atypical antipsychotics versus other psychotropic drugs [68]. The three studies found no increase in mortality with antipsychotics in patients with dementia. However, the studies had several methodological problems. These included examining subjects with permanent antipsychotic medication and not new users [31, 69], they were not controlling for exposure, [70–72], had problems with statistical power [70, 73], not controlling for other pharmacological treatments [70], and show varying lengths of follow-up periods [70].

More recently, a large retrospective cohort study examined the mortality risk associated with individual antipsychotics using various methods to control for confounding factors [53] (LoE 2b). It looked at a national sample of more than 33,000 older veterans with dementia newly started on haloperidol, risperidone, olanzapine, quetiapine, or valproic acid and derivatives (as a non-antipsychotic comparator compound). Mortality was highest in those receiving haloperidol (relative risk 1.54, 95% CI 1.38 to 1.73), followed by risperidone (reference, relative risk 1) and olanzapine (0.99, 95% CI 0.89 to 1.10), then valproic acid (0.91, 95% CI 0.78 to 1.06), and lastly quetiapine (0.73, 95% CI 0.67 to 0.80) [53]. These results were found across all analyses (intention to treat, exposure, dose adjusted, propensity adjusted). Other researches also indicated that in patients with Alzheimer's disease who had psychosis or agitation and had responded

to risperidone therapy for 4 to 8 months, discontinuation of the antipsychotic was associated with an increased risk of relapse (hazard ratio, 4.88; 95% CI 1.08 to 21.98; $p = 0.02$) [74] (LoE 2b). These findings are partly supported by a recent Cochrane Review [64] (LoE 1). The review concluded that many older people with Alzheimer's dementia and BPSD can be withdrawn from chronic antipsychotic medication without detrimental effects on their behavior. However, it remains uncertain whether withdrawal is beneficial for cognition or psychomotor status, but the results of this review suggest that discontinuation programs could be incorporated into routine practice. Two studies of people whose agitation or psychosis had previously responded well to antipsychotic treatment found an increased risk of relapse or shorter time to relapse after discontinuation. In contrast, two other studies suggest that people with more severe BPSD at baseline could benefit from continuing their antipsychotic medication. In these individuals, withdrawal might not be recommended [75].

Antidepressants

Tricyclic antidepressants have been shown to have limited benefit and a number of potential risks in the treatment of depression in dementia. An earlier meta-analysis (four RCTs) suggested that selective serotonin reuptake inhibitors (SSRIs) had good tolerability and a favorable treatment response (effect size -0.93 , 95% CI 3.27 to 1.41) [76] (LoE 1a), with a methodologically sound study indicating a good treatment response to sertraline (depression improvement effect size 0.68, $F = 1.41$, 10.9; $p = 0.002$) [77] (LoE 1b). However, a recent meta-analysis of five studies on SSRIs reported a lack of clear benefit for depression [23, 77–80] (LoE 1a). It reported that the 5 studies differed in terms of depression diagnostic criteria, tested drug, and outcome measures, which could have accounted for overall lack of clear benefit for depression (Within a random effect model, ES estimates of the first and second nested global analyses were non-significant, non-heterogeneous and small to null at the endpoint for depression, favoring SSRIs, -0.06 and -0.10 , respectively, $p > 0.05$).

Antidepressants have also been used to target agitation and psychosis in dementia. A review of such trials found evidence for a reduction in agitation with sertraline and citalopram compared with placebo (mean difference -0.89 (95% CI -1.22 to -0.57) [81] (LoE 1a). Most recently, the “Citalopram for Agitation in Alzheimer's Disease” (CITAD) study randomized 186 people with clinically significant agitation to receive psychosocial intervention plus citalopram (target dose of 30mg) or placebo for nine weeks [82] (LoE 1b). Individuals who were under citalopram treatment showed significant improvement over placebo on several clinical measures (including Clinical Global Impression of Change, odds ratio 2.13; 95% CI 1.23 to 3.69; $p = 0.02$) and lower caregiver's distress (-2.80 ; -4.94 to -0.47 ; $p = 0.020$) [7].

In an older review [69] (LoE 2a) the authors reported on five randomized controlled trials of antidepressants (sertraline, fluoxetine, citalopram, and trazodone)

in BPSD treatment. Of these five studies, only the citalopram trial showed any benefit [83] (LoE 2b). In this RCT, inpatients with at least one moderate-to-severe target symptom (aggression, agitation, hostility, suspiciousness, hallucinations, or delusions) were randomly assigned to receive citalopram, perphenazine or placebo for up to 17 days. Both the citalopram and perphenazine groups showed significant improvement from baseline with respect to agitation/aggression, psychosis, and lability/tension. The citalopram group also showed significant improvement in cognitive deficits. Persons receiving placebo did not demonstrate significant change in any BPSD symptoms. However, this trial had a high dropout rate, with more than half of patients in each group failing to complete the study, most commonly because of a lack of efficacy [54]. In a recent systematic review [84] (LoE 2a) a total of 19 randomized controlled trials that used an antidepressant medication for the treatment of BPSD was found. Of the 19 trials, 15 involved a selective serotonin reuptake inhibitor (SSRI) compound and four involved trazodone. Eight trials using an SSRI compound and three trials using trazodone showed benefit in the treatment of BPSD. The antidepressant drug was well tolerated in at least 14 of the 19 trials, with information about tolerability in one trial not provided in the study (paroxetine or placebo for frontotemporal dementia). These findings indicate that antidepressants can be effective in the treatment of BPSD and are generally well tolerated in elderly persons with dementia [84].

Side effects of antidepressants

Although safety considerations and current evidence favor SSRIs, adverse events do occur. These include nausea and vomiting; headaches; sleep changes; diarrhea; tremor; sexual dysfunction; hyponatremia, owing to the syndrome of inappropriate antidiuretic hormone secretion (in about 10% of patients) [85] (LoE 2b) and gastrointestinal bleeding. In CITAD, worsening of cognition and QT prolongation were also seen in the citalopram group [55] (LoE 1b), although only a small number of patients in this study met the gender specific threshold of QT prolongation (three in the drug group and one in the placebo group) [86] (LoE 1b). The FDA has issued a warning for QT prolongation and torsade de pointes with only citalopram (doses > 20 mg) among the SSRIs (Selective Serotonin reuptake inhibitors) and QT prolongation has been associated with all SSRIs. However, QT prolongation is associated with various medications, and the literature on the association between QT prolongation and arrhythmias such as torsade de pointes is mixed. A subsequent observational study found no increased risk of ventricular arrhythmia or cardiac mortality with citalopram or sertraline [6] (LoE 2b), [87] (LoE1b).

Anticonvulsants and related compounds

Again, in an older systematic review [88] (LoE 2a) three studies were identified which investigated the anticonvulsant valproate [89–91]. The authors concluded that, based on current evidence, valproate preparations cannot be recommended for the treatment of agitation in persons with dementia. In addition, a Cochrane database review of valproate for the treatment of agitation in persons with dementia indicates that low-dose sodium valproate is ineffective and that high-dose divalproex sodium is associated with an unacceptable rate of adverse effects (sedation – OR = 2.64; gastrointestinal disturbance – OR = 4.12; urinary tract infection – OR = 3.02; falls without injury – OR = 2.08) [92] (LoE 1a). The same conclusions were drawn in a systematic review [93] (LoE 2a). In an updated version of the above mentioned Cochrane review 2009, the authors concluded that, based on current evidence, valproate preparations cannot be recommended for the treatment of agitation in persons with dementia [92] (LoE 1a).

The same review [88] reported on two small, randomized controlled trials of carbamazepine for the treatment of BPSD [90, 94]. The first study was a 6-week, randomized, multisite, parallel-group study of nursing home patients with agitation and dementia. Participants were randomized to individualized doses of carbamazepine or to placebo [94] (LoE 2a). At 6 weeks, the mean daily dose of carbamazepine was 304 mg per day, and the mean serum level was 5.3 µg/mL. Over the study period, general global well-being ratings showed global improvement in 77% of patients taking carbamazepine and in 21% of patients taking placebo, and the BPSD symptoms decreased significantly more in the carbamazepine vs. control group [94]. The secondary analyses confirmed that positive changes were due to decreased agitation and aggression. Carbamazepine was generally well tolerated, and no changes in cognition or functional status were observed among participants. The authors also found that the perception of staff time needed to manage agitation showed a decrease for carbamazepine but not for placebo [95].

The second drug study was a 6-week, randomized, double-blind, placebo-controlled, parallel-group trial involving 21 persons with agitation (16 completers) who had been treated unsuccessfully with antipsychotics before randomization [96] (LoE 2a). Patients were randomized to carbamazepine (400 mg/day) or to placebo. The authors found greater improvement in general wellbeing than BPSD like hostility in the group taking carbamazepine; however, there was a statistical trend toward worsening of hallucinations in persons taking carbamazepine. Overall, the drug demonstrated modest clinical benefit in these patients, with particular benefit in reducing hostility. Adverse events from the drug were mild in severity, occurring in four of nine carbamazepine-treated persons and eight of 12 placebo-treated persons. Of the 13 adverse events reported in the carbamazepine-treated group, diarrhea was the most common, occurring in three subjects intermittently for less than 2 weeks. Of the 18 adverse events reported among persons receiving placebo, vomiting was the most common, occurring in two subjects [93]. Based on the findings of these two trials [94, 96] along with the fact

that there is a Black Box warning on hematologic toxicity for carbamazepine (FDA 2006) and on potential drug-drug interactions between carbamazepine and other drugs commonly prescribed to elderly individuals, there is insufficient evidence of benefit to recommend the routine use of carbamazepine in the treatment of BPSD. Data for other anticonvulsants are scarce.

Psychopharmacological treatment – other compounds

Cholinesterase inhibitors and memantine

Although a meta-analysis showed a small but significant improvement in BPSD with cholinesterase inhibitors over placebo during six months of treatment, the improvement may not be clinically significant (summary estimate 1.72-point improvement vs. placebo on the 120-point Neuropsychiatric Inventory (NPI) scale; 0.87 to 2.57) [97] (LoE 2a). Furthermore, the treatment effect was driven by two studies of metrifonate, which has never been approved by the FDA in the US owing to concerns about toxicity [72] (LoE 2a). Previously, systematic reviews and meta-analyses [69] (LoE 1a), [89] (LoE 1a), [12] (LoE 2a) and six randomized controlled trials of various cholinesterase inhibitors with neuropsychiatric symptom outcomes were conducted. Five of the studies reported statistically significant benefit regarding BPSD improvement with these medications [47].

Two meta-analyses included two trials of galantamine that provided data for BPSD using the Neuropsychiatric Inventory (NPI) total scores [97, 98] (LoE 1a). The 3-month trial failed to reach statistical significance, while the 6-month trial demonstrated statistically significant results in favor of treatment with galantamine at daily doses of 16 mg. In general, galantamine appeared to be well tolerated but, as expected, tended to produce a higher frequency of gastrointestinal adverse events. In the second meta-analysis, the investigators found that patients randomized to cholinesterase inhibitors (donepezil, galantamine, metrifonate, physostigmine, tacrine, and velnacrine), of which some but not all are FDA and EMA approved for dementia treatment. For neuropsychiatric outcomes, 10 trials included the ADAS-NonCog (Alzheimer's Disease Assessment Scale – Noncognitive) and 6 included the NPI. Compared with placebo, patients randomized to cholinesterase inhibitors improved 1.72 points on the NPI (95% CI 0.87–2.57 points), and 0.03 points on the ADAS-NonCog (95% CI 0.00–0.05 points). For functional outcomes, 14 trials used ADL and 13 trials used IADL scales. Compared with placebo, patients randomized to cholinesterase inhibitors improved 0.1 SDs on ADL scales (95% CI 0.00–0.19 SDs), and 0.09 SDs on IADL scales (95% CI 0.01 to 0.17 SDs). There was no difference in efficacy among various cholinesterase inhibitors [47].

In addition, donepezil showed no benefit for clinically significant agitation over 12 weeks in a large RCT [47] (LoE 1b), or for overall change in Neuropsychiatric Inventory scores in a longer term trial with up to 4-year follow-up [99].

It has been suggested that cholinesterase inhibitors improve psychotic symptoms in Lewy body dementia [6]. However, a RCT found no difference between rivastigmine and placebo on overall BPSD or on a “Lewy body cluster” of symptoms (delusions, hallucinations, apathy, and depression) [100] (LoE 1b). Although one RCT in Parkinson’s disease dementia found no significant improvement in behavior with donepezil over placebo [101] (LoE 1b), a recent systematic review found that the use of cholinesterase inhibitors in this disease had a positive impact on behavioral and psychological symptoms of dementia (-0.20 , 95% CI -0.36 to -0.06 ; $p = 0.01$). However, use of cholinesterase inhibitors was associated with an increased risk of parkinsonian symptoms, such as tremor [102] (LoE 1a).

Although data from RCTs of memantine in patients with moderate to severe dementia had indicated that it might also confer benefit [21] (LoE 2a), [103] (LoE 1a) [92] (LoE 2a), a recent trial specifically examining the efficacy of this agent for Alzheimer’s dementia with agitation found no benefit over placebo [104] (LoE 1b).

A meta-analysis reported that although memantine may be of benefit in cognitive and functional domains, it does not appear to provide a clinically significant benefit in the treatment of BPSD in patients with moderate-to-severe AD [88] (LoE 1a). A previous database analysis of two randomized studies regarding the effects of memantine treatment on BPSD found that, in both studies, the improvement of these symptoms at end point was consistently in favor of treatment with memantine as compared with placebo and donepezil, reaching statistical significance in the study of combination therapy with memantine and donepezil ($p = 0.02$) [105] (LoE 2b). The authors concluded that memantine has a beneficial effect on the behavioral symptoms of patients with moderate-to-severe AD, with the most pronounced effect found in the agitation/aggression behaviors [105]. A 2008 meta-analysis included six randomized, parallel-group, double-blind studies that included subjects with BPSD; improvement [106] (LoE 2b) data on BPSD outcomes were available for five of the six studies. In those five studies, patients taking memantine had a marginally significant improvement of BPSD as compared to the placebo group ($n = 868$ vs. $n = 882$) ($p = 0.041$). The authors pointed out that there are a number of limitations with the current data, including the relatively small effect size for memantine, and concluded that it is unclear at the present time whether memantine produces significant clinical benefit [106]. Although data from these RCTs of memantine in patients with moderate-to-severe dementia had indicated that it might also confer benefit [105, 106], a recent trial specifically examining the efficacy of this agent for Alzheimer’s dementia with agitation found no benefit over placebo [104] (LoE 1b).

Adverse events with cholinesterase inhibitors and memantine

Cholinesterase inhibitors are associated with diarrhea, nausea, and vomiting, and less commonly with symptomatic bradycardia and syncope [104] (LoE 1b), [103]

(LoE 1a). These drugs should therefore be used with caution in people with low resting heart rates. Memantine has been associated with dizziness, headache, confusion, and constipation [107].

Other compounds – benzodiazepines

In the only double-blind study of a benzodiazepine compound to treat BPSD, [108] (LoE 2b) compared the efficacy and safety of intramuscular olanzapine, lorazepam, and placebo in treating agitation associated with AD and/or vascular dementia. The investigators found that, 2 hours after application (short term), olanzapine (5 mg and 2.5 mg) and lorazepam (1 mg) showed significant improvements over placebo on psychotic symptoms and agitation. At 24 hours, olanzapine (5 mg and 2.5 mg) maintained superiority over placebo on psychotic symptoms, but lorazepam (1 mg) did not. Sedation and other adverse events were not significantly different between both compounds and placebo [109] (LoE 4).

Adverse events with benzodiazepines

Benzodiazepines are associated with excessive sedation, lack of coordination, dizziness, falls, worsened cognition, respiratory depression, possible dependency and withdrawal, and occasionally paradoxical disinhibition [110] (LoE 4).

Summary of drug treatments

Of all agents currently used for behavioral and psychological symptoms of dementia, atypical antipsychotics have the strongest evidence base, although their benefits are moderate at best (effect size 0.16–0.31) [6] (LoE 2a). Any such benefits must be balanced against the risk of adverse events, including mortality. The mortality findings among individual antipsychotic agents seem to be consistent with the tolerability profile of individual atypical antipsychotics in the CATIE-AD trial, where olanzapine and risperidone were more efficacious than either quetiapine or placebo, but quetiapine and placebo were better tolerated [52] (LoE 2b). Thus, although quetiapine (and valproic acid) may have a better safety profile than olanzapine and risperidone, this fact needs to be balanced against their reduced efficacy. This reflects the pros and cons that confront clinicians prescribing antipsychotics for these patients. Antidepressants have shown limited benefit for depression in dementia. However, it has been theorized that because clinical trials often exclude severely depressed patients, the apparent treatment benefit may be reduced [63] (LoE 3a). Recent evidence indicates that citalopram may hold promise for the treatment of agitation in dementia, but more research is needed to determine the optimal dose given concerns about possible QT prolongation at 30 mg [6] (LoE 2a). The use of memantine and cholinesterase

inhibitors for BPSD treatment, however, is controversial and studies do not report a unanimous improvement of BPSD.

Again, before treatment with antipsychotics or antidepressants is considered, non-pharmacological methods should be employed. These approaches, including reminiscence therapy, caregiver training in behavioral management techniques, therapeutic activities, specialized dementia units, and simulated presence interventions or reduced stimulation units were noted to merit further study due to little or no convincing evidence, inconsistent outcomes, mixed evidence, and contradictory or inconclusive findings [111] (LoE 2a).

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