Annals of Internal Medicine REVIEW

Comparative Efficacy of Interventions for Aggressive and Agitated Behaviors in Dementia

A Systematic Review and Network Meta-analysis

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Background: Both pharmacologic and nonpharmacologic interventions are used to treat neuropsychiatric symptoms in persons with dementia.

Purpose: To summarize the comparative efficacy of pharmacologic and nonpharmacologic interventions for treating aggression and agitation in adults with dementia.

Data Sources: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, and PsycINFO between inception and 28 May 2019 without language restrictions; gray literature; and reference lists scanned from selected studies and systematic reviews.

Study Selection: Randomized controlled trials comparing interventions for treating aggression and agitation in adults with dementia.

Data Extraction: Pairs of reviewers independently screened studies, abstracted data, and appraised risk of bias.

Data Synthesis: After screening of 19 684 citations, 163 studies (23 143 patients) were included in network meta-analyses. Analysis of interventions targeting aggression and agitation (148 studies [21 686 patients]) showed that multidisciplinary care (standardized mean difference [SMD], −0.5 [95% credible interval {CrI}, −0.99 to −0.01]), massage and touch therapy (SMD, −0.75 [CrI, −1.12 to −0.38]), and music combined with massage and touch therapy (SMD, −0.91 [CrI, −1.75 to −0.07]) were clinically more efficacious than usual care. Recreation therapy (SMD, −0.29 [CrI, −0.57 to −0.01]) was statistically but not clinically more efficacious than usual care.

Limitations: Forty-six percent of studies were at high risk of bias because of missing outcome data. Harms and costs of therapies were not evaluated.

Conclusion: Nonpharmacologic interventions seemed to be more efficacious than pharmacologic interventions for reducing aggression and agitation in adults with dementia.

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Dementia, which affects 50 million people worldwide, is characterized by progressive and deleterious effects on cognition and function (1, 2). As many as 75% of persons with dementia experience neuropsychiatric (behavioral and psychological) symptoms, including aggression, agitation, and anxiety (3, 4). Compared with those who do not have neuropsychiatric symptoms, these persons are institutionalized earlier and have poorer ability to complete activities of daily living (ADLs), greater cognitive decline, lower quality of life, and increased risk for death (5–7). In addition, their caregivers report worse quality of life than caregivers of patients without behavioral and psychiatric symptoms (8).

Both pharmacologic (for example, antipsychotics and antidepressants) and nonpharmacologic (for example, exercise and massage therapy) interventions are used to treat neuropsychiatric symptoms in dementia (9–12). Pharmacologic interventions have been associated with potential harms in this patient population, including falls, fractures, and death (13). However, rates of drug prescribing remain high despite guidelines supporting use of nonpharmacologic interventions first and initiatives aimed at deprescribing (14–17).

Our understanding of the comparative efficacy of pharmacologic and nonpharmacologic interventions for treating neuropsychiatric symptoms in dementia has been limited by a lack of head-to-head randomized controlled trials (RCTs). This incomplete understanding, coupled with the potential adverse outcomes associated with certain pharmacologic interventions, leads to uncertainty in decision making and variation in practice. Therefore, our objectives were to determine the comparative efficacy of pharmacologic and nonpharmacologic interventions and the best interventions for treating aggression and agitation in persons with dementia.

METHODS

We registered (PROSPERO: CRD42017050130) and published our protocol and followed established guidance for reporting systematic reviews incorporating network meta-analysis (NMA) (18, 19). The methods and protocol deviations are presented in Supplement Files 1, 2a, and 2b (all supplemental files, tables, and figures are available at Annals.org).

Data Sources and Searches

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, and

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PsycINFO for citations published in any language from inception until 28 May 2019. We also searched gray literature, reviewed reference lists of included studies and related systematic reviews, and searched MEDLINE from inception until 4 July 2019 for NMAs related to dementia care.

Study Selection

We included RCTs of pharmacologic or nonpharmacologic interventions used to treat aggression and agitation in persons with dementia. Pharmacologic interventions were limited to those with final approval from the U.S. Food and Drug Administration or Health Canada as of our literature search date. Eligible comparators were usual care or another pharmacologic or nonpharmacologic intervention.

Twelve dementia care partners (nurses, allied health professionals, physicians, and a caregiver) selected our study outcomes (18) by independently ranking a group of commonly reported neuropsychiatric symptoms (for example, aggression, agitation, and sleep disturbances) in descending order of importance. The care partners selected change in aggression as our main outcome and change in agitation as our secondary outcome. These are commonly classified further to identify the following specific aggressive or agitated behaviors: physical aggression, verbal aggression, combined physical and verbal aggression, physical agitation, verbal agitation, and combined aggression and agitation (incorporating physical aggression, verbal aggression, physical agitation, and verbal agitation as a single outcome) (20, 21). We included studies reporting these outcomes using any outcome measure (such as the Neuropsychiatric Inventory or the Cohen-Mansfield Agitation Inventory) (4, 21). We reviewed the components of each outcome measure in relation to the 4 factors described in the Cohen-Mansfield Agitation Inventory (physical aggression, verbal aggression, physical agitation, and verbal agitation) to determine the behaviors reported in each outcome measure (20). For example, if a scale reported both physically and verbally aggressive behaviors, we classified it as reporting "combined physical and verbal aggression" (**Supplement Table 1**) (21).

After pilot testing, pairs of reviewers (J.A.W., Z.G., V.N., P.A.K., M.G., and Y.T.) independently screened all citations and full-text articles to assess eligibility for inclusion. Discrepancies regarding study inclusion were resolved by deliberation within the reviewer pairs or with input from a third reviewer.

Data Abstraction and Quality Assessment

Pairs of reviewers (J.A.W., Z.G., V.N., P.A.K., M.G., and Y.T.) abstracted data from each included full-text article and appraised each study using the Cochrane Risk of Bias Tool (22). For studies that reported 2 or more measures for the same outcome, we established a hierarchy for determining the data to be abstracted (**Supplement File 2b**). We contacted study authors as appropriate for additional information about study design and reported outcome measures. Discrepancies regarding data abstraction and quality assessment were resolved by deliberation within the reviewer pairs or with input from a third reviewer.

Data Synthesis and Analysis

Two clinicians (J.A.W. and Z.G.) categorized and then coded the interventions (**Supplement Table 2**), with input from our dementia care partners; disagreements were resolved by a third clinician (S.E.S.). We assessed network connectivity by preparing network diagrams in Stata, version 15.1 (StataCorp) (23), and we assessed network transitivity by visually inspecting tables containing the number of patients per treatment comparison; the number of studies per treatment comparison; and the following study characteristics: study duration, patient age, proportion of women (≥50% or <50%), study setting (for example, nursing home or clinic), dementia type, outcome measure reported, history of neuropsychiatric symptoms, severity of dementia, and 2 items from the risk-of-bias assessment (incomplete outcome data and blinding of outcome assessment).

We conducted Bayesian shared parameter random-effects NMA for each outcome in OpenBUGS, version 3.2.3 (24). Informative prior distributions were implemented for all between-study heterogeneity parameters ($\log(\tau^2) \sim t(-3.85,1.932,5)$) (25). Vague prior distributions were implemented for trial baselines and treatment differences (N(0,1000)). Because several different scales were reported across studies, we report the outcomes as posterior standardized mean differences (SMDs) with associated 95% credible intervals (CrIs) and predictive intervals. We ranked treatments by using surface under the cumulative ranking curve (SUCRA) values (26), which were summarized across all treatments and outcomes in a rank-heat plot (27).

We assessed for global inconsistency by comparing deviance and deviance information criterion statistics between consistency and inconsistency models (28), and we assessed for local inconsistency in each closed network loop using the loop-specific approach (29). Subgroup analyses were conducted based on the following effect modifiers: residence in a nursing home or assisted living facility, whether mean age of the study population was at least 80 years or less than 80 years, whether the proportion of women was at least 50% or less than 50%, whether standardized criteria were used to diagnose dementia, study size (studies with <50 patients enrolled were omitted), and whether intervention duration was at least 11 weeks or less than 11 weeks. Meta-regression was performed based on publication year. We conducted sensitivity analyses based on the 2 components of the risk-of-bias assessment that represented the greatest threat to the validity of study findings: incomplete outcome data and blinding of outcome assessment. We also conducted a sensitivity analysis using a weakly informative prior distribution for heterogeneity ($\tau \sim N(0,1)$, $\tau > 0$) in our primary analyses. Using the *network* command in Stata, we assessed for publication bias with comparison-adjusted funnel plots (23). Treatments were ordered by expected efficacy (for example, recreation therapy would be expected to be

more efficacious than usual care). To facilitate clinical interpretation of our findings, we back-transformed SMDs to mean differences (MDs) measured by the Cohen-Mansfield Agitation Inventory and then compared these values with a minimum clinically important difference derived as per a distribution-based approach (30, 31).

Role of the Funding Source

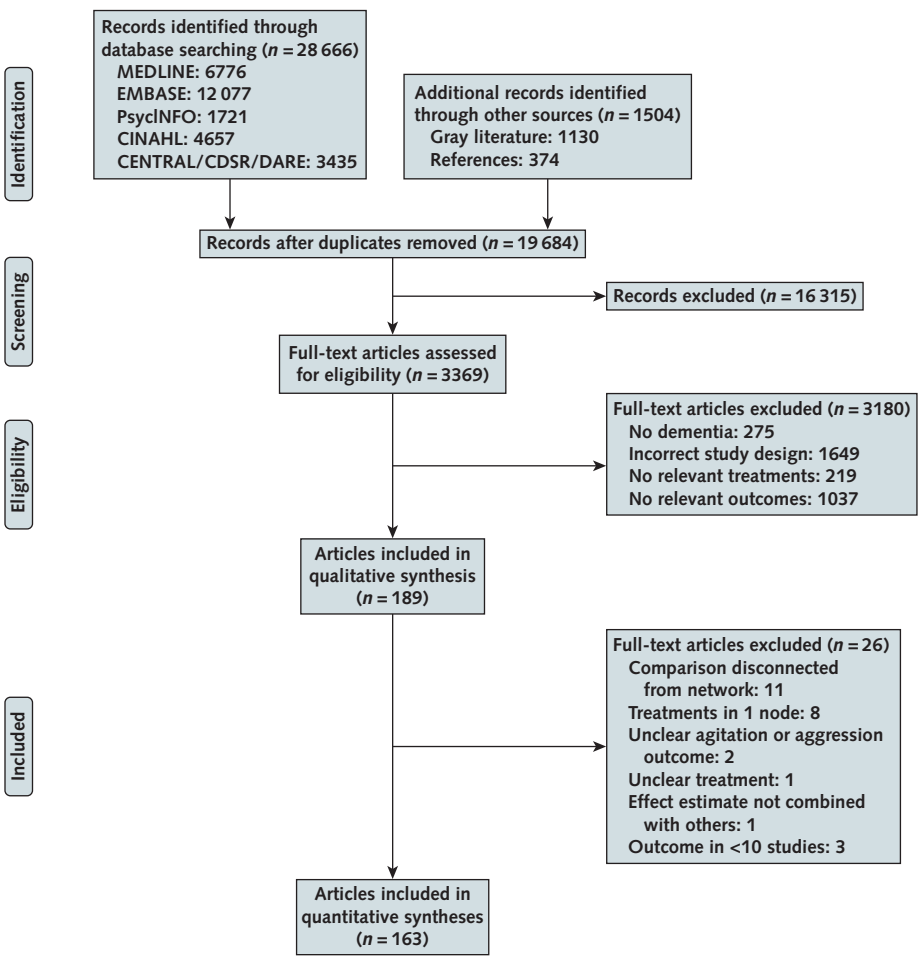
The Alberta Health Services Critical Care Strategic Clinical Network funded this study but had no role in its conception, design, conduct, analysis, or reporting; review of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

We screened 19 684 article titles and abstracts and 3369 full-text articles (Figure 1). We included 189 articles (25 736 persons with dementia) in our systematic review and 163 articles (23 143 persons with dementia) in our analysis (reference citations are provided in the Supplement). In 1 instance, different outcome measures of interest for the same study population were published in 2 separate articles (32, 33). Of the 33 authors we contacted for additional information, 14 (42%) responded, and 4 (29%) of these provided further data to include in the NMAs.

Table 1 summarizes study characteristics, and Supplement Tables 3 and 4 present individual-study characteristics and study-level patient characteristics, respectively. Almost all studies reported a mean patient age of 70 years or older, and most had at least 50% women (Table 1). Thirty-seven percent of studies did not report dementia type for their participants, 27.5% reported enrolling patients with Alzheimer disease, and 32.8% reported enrolling patients with different dementia types (such as vascular or mixed). Many studies did not specify the severity of dementia in participants or enrolled persons with any severity (mild, moderate, and severe). No studies enrolled patients with exclusively mild dementia. The majority of interventions (54.5%) were less than 11 weeks in duration. Forty-six percent of studies were judged to be at high risk of bias

Figure 1. Study flow diagram.



CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effects.

Table 1. Characteristics of 189 Studies Included in the Systematic Review

Characteristic	Studies, *n* (%)
Mean age of study participants	
<70 y	4 (2.1)
70–74.9 y	18 (9.5)
75–79.9 y	38 (20.1)
≥80 y	119 (63)
Not reported	10 (5.3)
Women enrolled in study	
0%–49%	20 (10.6)
50%–100%	154 (81.5)
Not reported	15 (7.9)
History of neuropsychiatric symptoms in study participants	
Yes	128 (67.7)
No	3 (1.6)
Not reported	58 (30.7)
Type of dementia in study participants	
Multiple (e.g., AD + VaD)	62 (32.8)
AD	52 (27.5)
PDD	1 (0.5)
FTD	4 (2.1)
Not reported	70 (37)
Dementia severity in study participants	
Mild/moderate	21 (11.1)
Mild/moderate/severe	51 (27)
Moderate	3 (1.6)
Moderate/severe	38 (20.1)
Severe	12 (6.3)
Not reported	64 (33.9)
Study setting	
Clinic/community	33 (17.5)
Hospital	11 (5.8)
Nursing home/assisted living facility	123 (65.1)
Multiple settings	16 (8.5)
Not reported/not clearly reported	6 (3.2)
Duration of study intervention	
<11 wk	103 (54.5)
11–20 wk	49 (25.9)
21–30 wk	18 (9.5)
>30 wk	12 (6.3)
Not reported	7 (3.7)

AD = Alzheimer disease; FTD = frontotemporal dementia; PDD = Parkinson disease dementia; VaD = vascular dementia.

due to missing outcome data; no other items were identified to be at high risk of bias (Supplement Figure 1 and Supplement Table 5).

Physical Aggression, Verbal Aggression, and Combined Physical and Verbal Aggression

Twenty-two studies (2780 patients; 18 treatment nodes) were included in the network of interventions targeting physical aggression, and 15 studies (1736 patients; 14 treatment nodes) were included in the network of interventions targeting verbal aggression. The networks for physical aggression and verbal aggression were connected (Supplement Figures 2a and 2b). The network for combined physical and verbal aggression was disconnected; therefore, we did not perform meta-analyses for this outcome (Supplement Figure 2c). Transitivity was maintained across treatment comparisons for the outcomes of physical aggression and verbal aggression (Supplement Tables 6a and 6b). Most treatment comparisons were at high risk of bias because of missing data, used a subscale of the Cohen-Mansfield Agitation Inventory as the outcome measure, and involved mostly women with dementia who were aged 80 years or older and living in a nursing home. Outcomes of pairwise and network meta-analyses compared with usual care are reported in Supplement Tables 7a and 7b. The common within-network, between-study variance was low in each NMA. There was no evidence of local or global inconsistency (Supplement Tables 7a and 7b and Supplement Figures 3a and 3b) and no evidence of potential small-study effects or publication bias (Supplement Figures 4a and 4b). The estimated minimum clinically important differences on the physical aggression and verbal aggression subscales of the Cohen-Mansfield Agitation Inventory were 3.23 and 3.03, respectively.

Outdoor activities were more efficacious than antipsychotics for treating physical aggression (Supplement Table 8a). Modification of ADLs, massage and touch therapy, and outdoor activities were all more efficacious than caregiver education for treating physical aggression. When a weakly informative prior distribution was used for between-study heterogeneity, ADL modification and outdoor activities remained more efficacious than caregiver education. For treating verbal aggression, massage and touch therapy was more efficacious than usual care, and ADL modification and massage and touch therapy were more efficacious than caregiver education and support (Supplement Table 8a). Results for treatment of verbal aggression were unchanged when we implemented a weakly informative prior distribution for between-study heterogeneity. Each of these SMDs was clinically important when reexpressed as the corresponding MD on the Cohen-Mansfield Agitation Inventory (Supplement Table 8a).

Physical Agitation, Verbal Agitation, and Combined Agitation and Aggression

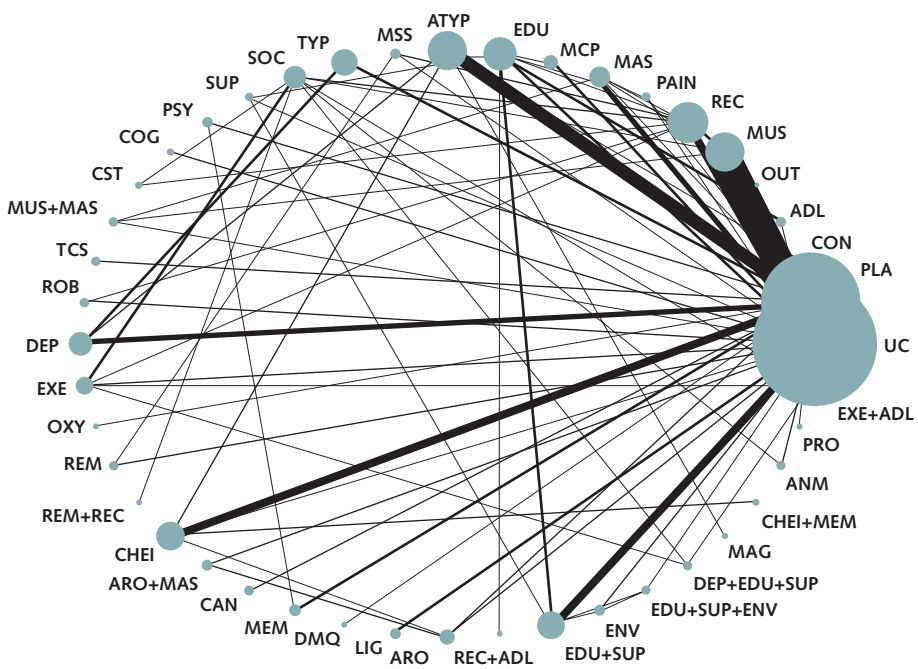
Twenty-six studies (2597 patients; 22 treatment nodes) were included in the network of interventions targeting physical agitation, 21 studies (2247 patients; 21 treatment nodes) were included in the network of interventions targeting verbal agitation, and 148 studies (21 686 patients; 44 treatment nodes) were included in the network of interventions targeting combined agitation and aggression. Each of the networks for physical agitation, verbal agitation, and combined agitation and aggression was connected (Figure 2 and Supplement Figures 2d and 2e). In the network plot for combined agitation and aggression (Figure 2), 64.8% of treatment comparisons involved usual care or placebo, and there were 46 triangular loops and 4 quadratic loops. Transitivity was maintained across treatment comparisons for each outcome (Supplement Tables 6c to 6e). Most treatment comparisons were at high risk of bias because of missing data, used the Cohen-Mansfield Agitation Inventory or one of its subscales (for physical or verbal agitation) as the outcome measure, and included mostly women with dementia

who were aged 80 years or older and living in a nursing home. The common within-network, between-study variance was low in each NMA. There was no evidence of local or global inconsistency (Supplement Tables 7c to 7e and Supplement Figures 3c to 3e). The estimated minimum clinically important difference on the physical agitation subscale of the Cohen-Mansfield Agitation Inventory was 3.01, and the minimum clinically important difference on the overall Cohen-Mansfield Agitation Inventory was 7.11.

Massage and touch therapy was more efficacious than usual care or caregiver education for treating physical agitation (Supplement Tables 7c and 8a). Each of the SMDs was estimated to be clinically important when reexpressed as the corresponding MD on the Cohen-Mansfield Agitation Inventory (Supplement Table 8a). No intervention was efficacious for treating verbal agitation (Supplement Table 7d). For the combined outcome of agitation and aggression, recreation therapy, multidisciplinary care, massage and touch therapy, and music combined with massage and touch therapy were more efficacious than usual care (Table 2 and Supplement Tables 7e and 8b). Except for the comparison between recreation therapy and usual care, each of these treatment comparisons for combined agitation and aggression was clinically important (Table 2 and Supplement Table 8b). When a weakly informative prior distribution was used for the common within-network, between-study heterogeneity, multidisciplinary care and recreation therapy were no longer efficacious relative to usual care for treating combined agitation and aggression. Comparison-adjusted funnel plots showed no evidence of publication bias (Supplement Figures 4c to 4e).

In a subgroup analysis of studies conducted in a nursing home or assisted living setting that reported the outcome of combined agitation and aggression (86 studies; 38 treatment nodes), music therapy and cognitive stimulation were also more efficacious than usual care (Table 3 and Supplement Table 9e). Several pharmacologic interventions were efficacious relative to placebo in the subgroup of studies using standard diagnostic criteria to diagnose dementia, but only cannabinoids and dextromethorphan–quinidine had a clinically important effect relative to placebo (Table 3). There was 1 inconsistent loop of evidence involving usual care, caregiver education, and caregiver support in the subgroup of studies conducted in nursing homes or assisted living facilities and enrolling persons aged

Figure 2. Network diagrams for network of interventions targeted at the combined outcome of agitation and aggression in persons with dementia.



Nodes represent individual interventions, and lines between nodes indicate that the interventions have previously been directly compared in a study. The nodes are weighted by the number of studies that evaluated the treatment, and the lines are weighted by the number of studies that evaluated the treatment comparison. ADL = modification of activities of daily living; ANM = animal therapy; ARO = aromatherapy; ATYP = atypical antipsychotics; CAN = cannabinoids; CHEI = cholinesterase inhibitor; COG = modification of instrumental activities of daily living; CON = anticonvulsants; CST = cognitive stimulation; DEP = antidepressants; DMQ = dextromethorphan–quinidine; EDU = caregiver education; ENV = environmental modification; EXE = exercise; LIG = light therapy; MAG = magnesium; MAS = massage and touch therapy; MCP = multidisciplinary care plan; MEM = memantine; MSS = multisensory stimulation; MUS = music therapy; OUT = outdoor activities; OXY = oxytocin; PAIN = pain management; PLA = placebo; PRO = propranolol; PSY = antipsychotics; REC = recreation therapy; REM = reminiscence therapy; ROB = robotic pet therapy; SOC = social interaction; SUP = caregiver support; TCS = transcutaneous stimulation; TYP = typical antipsychotics; UC = usual care.

Table 2. Efficacious Interventions for the Combined Outcome of Aggression and Agitation in Persons With Dementia

Treatment Comparison	MA Estimate of Studies (Participants), *n**	NMA SMD (95% CrI)	MA SMD (95% CrI)	NMA SMD Reexpressed as MD on CMAI†
ADL modification vs. IADL modification	–	−1.1 (−2.14 to −0.05)	–	−15.64
Antipsychotics vs. IADL modification	–	−1.18 (−2.26 to −0.07)	–	−16.78
Cannabinoids vs. IADL modification	–	−1.51 (−2.72 to −0.29)	–	−21.47
Caregiver education + support vs. IADL modification	–	−0.99 (−1.86 to −0.11)	–	−14.08
Caregiver education vs. IADL modification	–	−1.02 (−1.91 to −0.13)	–	−14.50
Cognitive stimulation vs. IADL modification	–	−1.27 (−2.4 to −0.11)	–	−18.06
Dextromethorphan–quinidine vs. IADL modification	–	−1.5 (−2.78 to −0.2)	–	−21.33
Environmental modification vs. IADL modification	–	−1.24 (−2.27 to −0.22)	–	−17.63
Exercise vs. IADL modification	–	−0.98 (−1.89 to −0.04)	–	−13.94
Massage and touch therapy vs. aromatherapy	–	−0.74 (−1.39 to −0.1)	–	−10.52
Massage and touch therapy vs. caregiver education and support	–	−0.52 (−1.02 to −0.02)	–	−7.39
Massage and touch therapy vs. caregiver support	–	−0.92 (−1.84 to −0.01)	–	−13.08
Massage and touch therapy vs. cholinesterase inhibitors	–	−0.7 (−1.32 to −0.07)	–	−9.95
Massage and touch therapy vs. IADL modification	–	−1.51 (−2.4 to −0.62)	–	−21.47
Massage and touch therapy vs. light therapy	–	−0.67 (−1.29 to −0.05)	–	−9.53
Massage and touch therapy vs. music therapy	1 (34)	−0.52 (−0.96 to −0.08)	0.01 (−0.65 to 0.67)	−7.39
Massage and touch therapy vs. placebo	1 (80)	−0.61 (−1.19 to −0.01)	0.21 (−0.23 to 0.64)	−8.67
Massage and touch therapy vs. recreation therapy	1 (81)	−0.45 (−0.91 to −0.01)	0.07 (−0.36 to 0.5)	−6.40
Massage and touch therapy vs. social interaction	–	−0.64 (−1.22 to −0.06)	–	−9.10
Massage and touch therapy vs. usual care	6 (385)	−0.75 (−1.12 to −0.38)	−0.9 (−1.28 to −0.51)	−10.67
Memantine vs. IADL modification	–	−1.12 (−2.16 to −0.06)	–	−15.93
Multidisciplinary care plan vs. IADL modification	–	−1.26 (−2.2 to −0.31)	–	−17.92
Multidisciplinary care plan vs. usual care	4 (552)	−0.5 (−0.99 to −0.01)	−0.44 (−1 to 0.12)	−7.11
Multisensory stimulation vs. IADL modification	–	−1.22 (−2.27 to −0.18)	–	−17.35
Music therapy + massage and touch therapy vs. IADL modification	–	−1.67 (−2.85 to −0.49)	–	−23.75
Music therapy + massage and touch therapy vs. usual care	1 (34)	−0.91 (−1.75 to −0.07)	−1.71 (−2.36 to −1.05)	−12.94
Music therapy vs. IADL modification	–	−0.99 (−1.84 to −0.14)	–	−14.08
Outdoor activities vs. IADL modification	–	−1.78 (−3.39 to −0.17)	–	−25.31
Recreation therapy vs. IADL modification	–	−1.05 (−1.9 to −0.2)	–	−14.93
Recreation therapy vs. usual care	8 (474)	−0.29 (−0.57 to −0.01)	−0.26 (−0.64 to 0.12)	−4.12
Typical antipsychotics vs. IADL modification	–	−1.14 (−2.17 to −0.09)	–	−16.21

ADL = activities of daily living; CMAI = Cohen-Mansfield Agitation Inventory; CrI = credible interval; IADL = instrumental activities of daily living; MA = pairwise meta-analysis; MD = mean difference; NMA = network meta-analysis; SMD = standardized mean difference.
* Sample size adjusted for clustering when appropriate.
† Minimum clinically important difference estimated to be 5.69 at 0.4 SD and 7.11 at 0.5 SD.

80 years or older with dementia (Supplement Figures 3f and 3g).

Treatment Rankings

In our primary analyses, outdoor activities ranked highest for combined aggression and agitation (SUCRA, 95% [95% CrI, 7% to 100%]) and physical aggression (SUCRA, 100% [CrI, 35% to 100%]). Outdoor activities (SUCRA, 92% [CrI, 8% to 100%]) and massage and touch therapy (SUCRA, 92% [CrI, 38% to 100%]) were the most highly ranked treatments for verbal aggression. Exercise combined with ADL modification ranked highest for physical agitation (SUCRA, 90% [CrI, 19% to 100%]), and anticonvulsants ranked highest for verbal agitation (SUCRA, 90% [CrI, 10% to 100%]) (Figure 3). These rankings were unchanged in our sensitivity analyses. Nonpharmacologic interventions were the most highly ranked interventions in all subgroups except the one using standard diagnostic criteria to diagnose dementia, in which dextromethorphan–quinidine ranked highest for treating combined aggression and agitation (SUCRA, 94% [CrI, 52% to 100%]).

Discussion

Across 5 outcomes of treatment efficacy for aggression and agitation in persons with dementia, 3 nonpharmacologic interventions were clinically efficacious compared with usual care: multidisciplinary care, massage and touch therapy, and music combined with massage and touch therapy. Although certain pharmacologic interventions (dextromethorphan–quinidine and cannabinoids) were efficacious relative to placebo or usual care in subgroup analyses, some nonpharmacologic interventions in these analyses also showed clinically important effects relative to placebo or usual care. Nonpharmacologic interventions may be efficacious because behavior has meaning, which needs to be uncovered through multidisciplinary assessments and care that addresses underlying needs (34). Our findings have important implications for persons with dementia and their care partners, suggesting that greater emphasis should be placed on nonpharmacologic approaches for treatment of aggression and agitation in persons with dementia.

We used NMA to fill a knowledge gap created by a lack of head-to-head studies in the literature (35). For example, we incorporated indirect evidence to show that multidisciplinary care is a clinically important intervention for treating agitation and aggression. Furthermore, our rank-heat plot will allow knowledge users or decision makers to quickly visualize the most highly ranked interventions for each targeted behavior,

thereby allowing tailoring of the evidence. We used NMA to identify nonpharmacologic interventions that could be associated with fewer potential harms than antipsychotics (13, 16, 36). These results will facilitate informed decision making by patients, caregivers, clinicians, and policymakers.

Our NMA comprehensively describes the comparative efficacy of pharmacologic and nonpharmacologic interventions for treating aggression and agitation in persons with dementia. Three published NMAs have described the efficacy of such interventions, but only 1 of these included nonpharmacologic interventions (37–39). However, except for exercise, that study omitted all of the nonpharmacologic interventions that we found to be efficacious in our primary analyses (39). Furthermore, none of these previous NMAs synthesized outcome measures from all available data; their analyses either were based on only 1 outcome measure (the Cohen-Mansfield Agitation Inventory) or included only certain outcome measures for aggression and agitation (37–39).

Our findings have potential limitations. First, some areas of the networks were sparse (Figure 2) (25). Second, several RCTs had 1 or more domains at unclear or high risk of bias. Given the particular concern about blinding of participants and assessors in RCTs of nonpharmacologic interventions, if authors did not indicate specifically who was blinded, we rated that domain as unclear in our NMAs. Third, because the majority of studies included patients with multiple types of dementia or did not specify the type among enrolled participants, we were unable to describe the efficacy of interventions in persons with specific types of dementia. Also, most studies did not address the presence or absence of delirium among participants. Fourth, potential effect modifiers, such as the number of interventions that had been tried before participants enrolled in the study, were not specified. Fifth, most studies did not focus on violent or extremely aggressive behavior; therefore, the comparative efficacy of interventions under these circumstances remains unclear. Finally, this systematic review did not explicitly assess adherence, harms, or costs associated with interventions.

In conclusion, we identified nonpharmacologic interventions that can be used instead of pharmacologic interventions for treating aggression and agitation in persons with dementia. These persons and their care partners should consider prioritizing nonpharmaco-

Table 3. Selected Subgroup Analyses: Efficacious Interventions (Compared With Usual Care or Placebo) for the Combined Outcome of Aggression and Agitation in Persons With Dementia

Treatment Comparison, by Subgroup	MA Estimate of Studies (Participants), *n**	NMA SMD (95% CrI)	MA SMD (95% CrI)	NMA SMD Reexpressed as MD on CMAI†
Intervention in long-term care/assisted living facilities				
Cognitive stimulation vs. usual care	–	−0.94 (−1.83 to −0.04)	–	−13.37
Massage and touch therapy vs. usual care	6 (385)	−0.76 (−1.06 to −0.46)	−0.87 (−1.18 to −0.58)	−10.81
Multidisciplinary care plan vs. usual care	3 (520)	−0.49 (−0.93 to −0.05)	−0.39 (−0.92 to 0.15)	−6.97
Music therapy vs. usual care	10 (460)	−0.31 (−0.55 to −0.08)	−0.37 (−0.63 to −0.11)	−4.41
Music therapy + massage and touch therapy vs. usual care	1 (34)	−0.95 (−1.63 to −0.27)	−1.7 (−2.36 to −1.05)	−13.51
Recreation therapy vs. usual care	5 (339)	−0.36 (−0.63 to −0.09)	−0.24 (−0.6 to 0.13)	−5.12
Mean age of study participants ≥80 y				
Anticonvulsants vs. usual care	–	−0.61 (−1.2 to −0.03)	–	−8.67
Massage and touch therapy vs. usual care	6 (328)	−0.77 (−1.08 to −0.46)	−0.88 (−1.22 to −0.56)	−10.95
Multidisciplinary care plan vs. usual care	3 (279)	−0.49 (−0.95 to −0.03)	−0.38 (−0.96 to 0.2)	−6.97
Music therapy vs. usual care	12 (535)	−0.26 (−0.49 to −0.02)	−0.26 (−0.52 to 0)	−3.70
Music therapy + massage and touch therapy vs. usual care	1 (34)	−0.93 (−1.63 to −0.22)	−1.71 (−2.36 to −1.05)	−13.22
Recreation therapy vs. usual care	8 (474)	−0.34 (−0.6 to −0.07)	−0.27 (−0.59 to 0.06)	−4.83
Typical antipsychotics vs. usual care	–	−0.65 (−1.26 to −0.06)	–	−9.24
>50% of study participants female				
Massage and touch therapy vs. placebo	1 (80)	−0.81 (−1.47 to −0.13)	0.21 (−0.23 to 0.64)	−11.52
Massage and touch therapy vs. usual care	5 (291)	−0.89 (−1.33 to −0.45)	−1.07 (−1.5 to −0.64)	−12.66
Music therapy + massage and touch therapy vs. usual care	1 (34)	−0.96 (−1.84 to −0.08)	−1.7 (−2.36 to −1.05)	−13.65
Standard diagnostic criteria used to diagnose dementia				
Antipsychotics vs. placebo	3 (167)	−0.39 (−0.73 to −0.02)	−0.13 (−0.69 to 0.44)	−5.55
Atypical antipsychotics vs. placebo	9 (2777)	−0.18 (−0.32 to −0.07)	−0.25 (−0.5 to 0.01)	−2.56
Cannabinoids vs. placebo	3 (397)	−0.52 (−1.02 to −0.03)	−0.29 (−0.66 to 0.07)	−7.39
Dextromethorphan–quinidine vs. placebo	1 (218)	−0.59 (−1.01 to −0.19)	−0.45 (−1.72 to 0.81)	−8.39
Memantine vs. placebo	4 (990)	−0.25 (−0.44 to −0.05)	−0.17 (−0.41 to 0.08)	−3.56
Music therapy vs. usual care	7 (341)	−0.3 (−0.54 to −0.05)	−0.26 (−0.63 to 0.1)	−4.27
Recreation therapy vs. usual care	–	−0.45 (−0.87 to −0.03)	–	−6.40
Typical antipsychotics vs. placebo	3 (418)	−0.26 (−0.49 to −0.05)	−0.14 (−0.64 to 0.37)	−3.70

CMAI = Cohen-Mansfield Agitation Inventory; CrI = credible interval; MA = pairwise meta-analysis; MD = mean difference; NMA = network meta-analysis; SMD = standardized mean difference.
* Sample size adjusted for clustering when appropriate.
† Minimum clinically important difference estimated to be 5.69 at 0.4 SD and 7.11 at 0.5 SD.

Figure 3. Rank-heat plot of SUCRA values for interventions targeting physical aggression, verbal aggression, physical agitation, verbal agitation, and combined agitation and aggression in persons with dementia.

The scale bar represents the SUCRA value for each intervention, with red indicating the lowest values (worst/least efficacious treatments) and green indicating the highest values (best/most efficacious treatments). ADL = modification of activities of daily living; ANM = animal therapy; ARO = aromatherapy; ATYP = atypical antipsychotics; CAN = cannabinoids; CHEI = cholinesterase inhibitor; CON = anticonvulsants; CST = cognitive stimulation; DEP = antidepressants; DMQ = dextromethorphan–quinidine; EDU = caregiver education; ENV = environmental modification; EXE = exercise; HRT = hormonal therapy; IADL = instrumental activities of daily living; LIG = light therapy; MAG = magnesium; MAS = massage and touch therapy; MCP = multidisciplinary care plan; MEM = memantine; MSS = multisensory stimulation; MUS = music therapy; OUT = outdoor activities; OXY = oxytocin; PAIN = pain management; PLA = placebo; PRO = propranolol; PSY = antipsychotics; QIP = quality improvement project; REC = recreation therapy; REM = reminiscence therapy; ROB = robotic pet therapy; SOC = social interaction; SUCRA = surface under the cumulative ranking curve; SUP = caregiver support; TCS = transcutaneous stimulation; TYP = typical antipsychotics; UC = usual care.
* Treatment without data on the outcome within the circle.

logic over pharmacologic interventions for aggression and agitation, given the potential harms associated with certain pharmacologic interventions (13, 36, 40). Policymakers should consider instituting and promoting policies to facilitate use of nonpharmacologic interventions. Research is needed to better understand the influence of individual-patient characteristics (via NMA based on individual-patient data) and the comparative cost-effectiveness of pharmacologic and nonpharmacologic interventions for treating aggression and agitation in persons with dementia (41).

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