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Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial

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ABSTRACT

Objective: *To investigate the impact of medication reviews using collegial mentoring and systematic clinical evaluation on psychotropic prescriptions, behavioral and psychological symptoms of dementia (BPSD), and activities of daily living (ADL).* ***Design:*** *Four-month multicenter, multicomponent, cluster-randomized, single-blinded controlled trial.* ***Setting:*** *Thirty-three Norwegian nursing homes including 67 nursing home wards (clusters).* ***Participants:*** *A total of 723 enrolled patients, of which 428 participated in the study; 217 were randomized to the intervention and 211 to care as usual (control).* ***Intervention:*** *The COSMOS intervention consisted of Communication, Systematic pain management, Medication reviews, Organization of activities, and Safety. During medication review, the nursing home physician evaluated treatment with colleagues systematically using the results from validated clinical assessments.* ***Measurements:*** *Mean changes from baseline to month 4 in the number of prescribed psychotropic drugs*

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(antipsychotics, anxiolytics, hypnotics or sedatives, antidepressants, and antidementia drugs); Neuropsychiatric Inventory Nursing Home Version (NPI-NH) and Cornell Scale of Depression in Dementia (CSDD); Lawton and Brody's Physical Self Maintenance Scale (PSMS). ***Results:*** *Compared to control, the mean change in prescribed psychotropic drugs was reduced both in total and regular number, while mean changes in NPI-NH and CSDD scores did not differ between the groups. Mean change in PSMS showed improvement in the intervention group, and deterioration in the control group.* ***Conclusion:*** *Medication reviews using collegial mentoring and systematic clinical evaluation led to safe deprescribing, as the reductions in psychotropic drug use did not negatively affect BPSD, while ADL improved.* (Am J Geriatr Psychiatry 2021; 29:304–315)

OBJECTIVE

The introduction of psychotropic drugs in the 1950s revolutionized the understanding and treatment of severe psychiatric disorders, undoubtedly alleviating the symptom burden and improving daily functioning for persons with severe affective and psychotic disorders.[1] Today, these drugs are often used off-label, thus the use of psychotropic drugs for managing behavioral and psychological symptoms of dementia (BPSD) warrants special attention.[2–5] BPSD such as delusions, hallucinations, agitation, anxiety, and aberrant motor behavior are associated with poorer physical and cognitive functioning as symptoms persist and reoccur in the course of dementia.[2,6–8] Nonpharmacological approaches are the preferred first-line treatment, although severe and persistent symptoms may require pharmacological therapy.[2] However, treating BPSD with multiple psychotropic drugs like antipsychotics, anxiolytics, hypnotics or sedatives, and antidepressants often has limited therapeutic effect and compromises activities of daily living (ADL), and may even cause adverse, potentially fatal, side effects for elderly patients.[2,3,7–9]

In recent years, several clinical trials have aimed at optimization and reduction of psychotropic drug use in nursing home patients.[5,9–13] These interventions typically addressed antidepressant and antipsychotic drug use, with varying strategies, designs, and outcome measures. Concomitantly, the term deprescribing gradually developed and is now regarded as part of the prescription continuum for proactive, patient-centered therapy.[14] Reeve et al. defined deprescribing as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes."[14] A recent systematic review on randomized controlled trials (RCTs) identified psychotropic drugs as the least responsive to deprescribing interventions among medications prescribed for chronic psychiatric and somatic conditions.[15] Further, it highlighted individualized drug recommendations and clinical assessments as necessary for the detection of symptom exacerbation and adverse effects to success with deprescribing. Even so, no previous RCT has explored the process of deprescribing as applied to all major groups of psychotropic drugs, while additionally evaluating the clinically relevant impact on BPSD and ADL.

Gulla et al. developed a method for interprofessional medication reviews using collegial mentoring and systematic clinical evaluation in nursing homes.[16] They implemented this strategy as a key component of the COSMOS trial, a multicomponent RCT, which also focused on communication, pain management, activities, and safety for nursing home patients.[17] In this study, we aim to investigate the effect of medication reviews on mean changes in the number of prescribed psychotropic drugs by using collegial mentoring and systematic clinical evaluation in the COSMOS trial, as well as explore if and how this approach is associated with changes in BPSD and ADL.

METHODS

This study presents secondary analyses of the 4-month multicenter, multicomponent, cluster-randomized, single-blinded controlled COSMOS trial.

Procedure

Intervention: The intervention consisted of five components, mirrored in the acronym COSMOS: Communication and advanced care planning, Systematic pain management, Medication reviews with collegial mentoring, Organization of activities adjusted to the individuals' need and preferences, and Safety. All the COSMOS components were implemented simultaneously in the nursing home units allocated to the intervention. The design, implementation process, and the primary outcome (Quality of Life) are described in detail elsewhere.[16–18]

The local nursing home physician performed the medication reviews together with a nurse and two research physicians (CG and BSH), who provided collegial mentoring. To structure the medication reviews, they utilized reports on validated assessment tools for the following: BPSD; ADL; pain; cognitive status and ability; well-being and quality of life; blood pressure; pulse; and body mass index.[16,17] The medical history including somatic and psychiatric diagnoses, as well as any laboratory test results requested by the nursing home physician, aided the revision of current drug use. A combination of the Norwegian Medical Agency's guidelines for medication reviews and the START or STOPP criteria, together with Duran et al.'s list of drugs with anticholinergic profiles available in Norway, assisted the medication reviews.[19–21] To detect drug interactions, nurses ran each patient's medication list through a database.[22] Nurses empowered patients and next of kin by incorporating their wishes and concerns into the medication reviews. The nursing home physician was responsible for medical treatment and any final decisions. An individual patient log tracked the clinical status and changes.

Control: Patients allocated to the control group received treatment as usual.

Sample

Nursing homes from eight municipalities of various size in Southern Norway were invited to participate in the COSMOS trial. The nursing home managers first authorized participation in the trial. Then a statistician randomized the units (clusters) of the participating nursing homes into an intervention and control group. Patients were recruited and included in the study from August 1, 2014 to March 15, 2015. Patients were followed for 4 months, with the last assessment on June 26, 2015. Patients aged ≥65 years with at least 2 weeks of residency in nursing homes were eligible. Exclusion criteria were schizophrenia and a life expectancy ≤ of 6 months.[17] Patients were lost at follow-up if they deceased or moved from the nursing home unit.

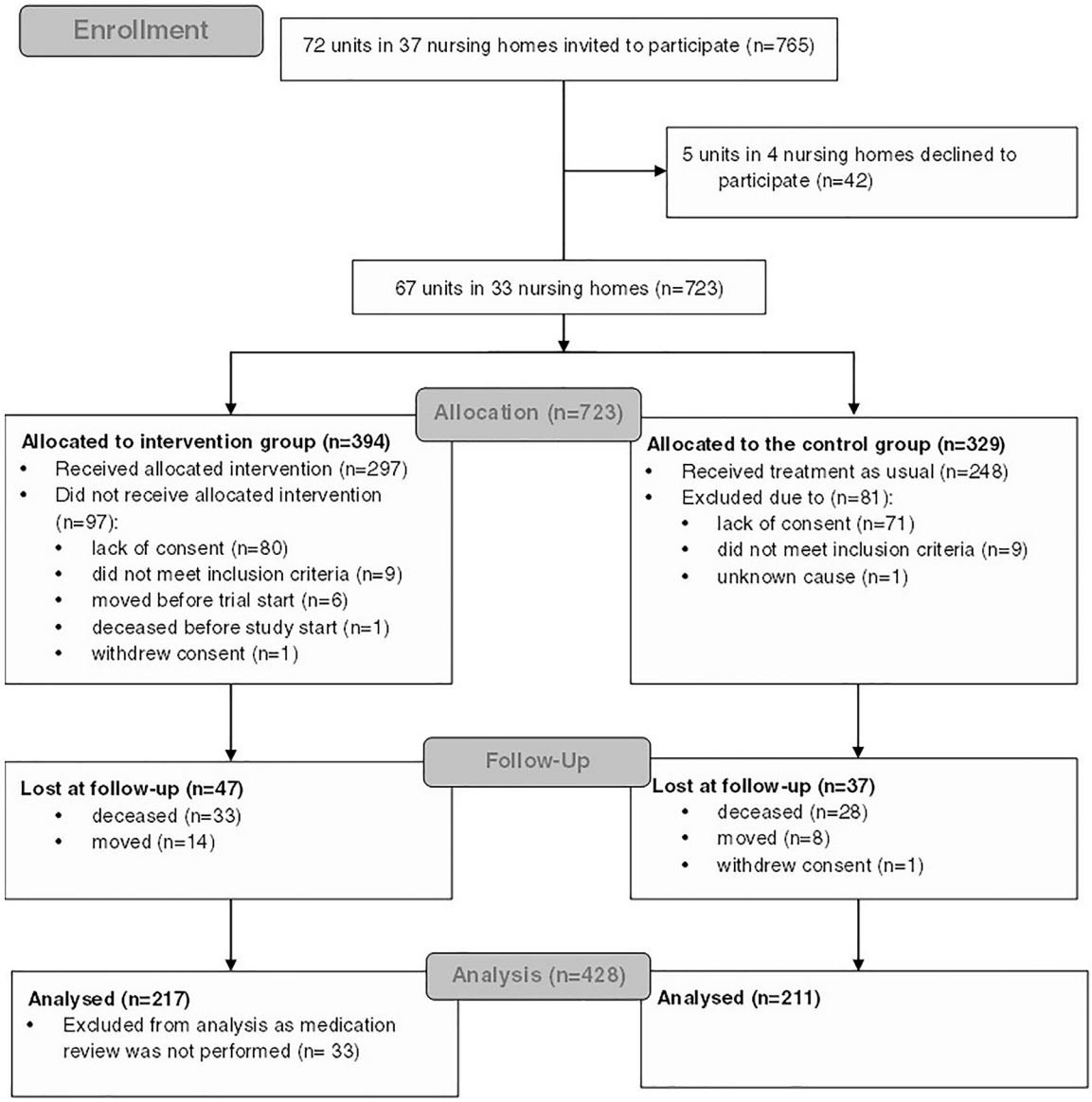
Of patients not lost to follow-up at 4 months, this study includes all controls and those patients in the intervention group who received medication reviews (Fig. 1: Flowchart). As shown in Figure 1, number of deceased patients were similar between the intervention and control group at 4 months follow-up.

Assessments

The primary outcome measure was mean change compared to baseline in numbers of prescribed psychotropic drugs, both in total and regularly at 4 months. The total number of prescribed drugs was the sum of regular and on-demand drug prescriptions of unique substances on the day of data collection. All drugs given on a set schedule counted as regularly prescribed drugs, and all others were considered on-demand. The following Anatomical Therapeutic Chemical Index classes qualified as psychotropic drugs: antipsychotics (N05A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D).[23]

The secondary outcome measures were mean changes in 1) BPSD estimated by the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) and the Cornell Scale for Depression in Dementia (CSDD), and 2) ADL evaluated by Physical Self Maintenance Scale (PSMS).[24–26] NPI-NH is a validated, proxy-rated instrument with high inter-rater reliability, determining the frequency (range: 1–4) and severity (range: 1–3) of 12 domains of BPSD over the preceding 4 weeks: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibitions, irritability, aberrant motorial behavior, sleep disturbances, and appetite changes.[24] The score for each domain is the frequency × severity product (range: 0–12), with domain scores ≥4 indicating symptoms of clinical relevance.[7] Adding the domain scores generates the NPI total score. CSDD is a proxy-rated instrument with good validity and reliability in screening persons with cognitive impairment or dementia for depression.[25] A total score of ≥8 indicates depression of clinical importance (range: 0–38). PSMS is valid and reliable for

FIGURE 1. Patient flow in the COSMOS trial; CONSORT 2010 flow diagram. CONSORT: Consolidated Standards of Reporting Standards; n: sample.



assessing each of the following six areas of ADL: feeding, dressing, grooming, physical ambulation, toileting, and showering.[26] Each area is rated on a five-point scale from full independence to full dependence (range: 6−30).

The *other variables* − age, sex, diagnoses by The International Classification of Primary Care, and the mini-mental status evaluation (MMSE) − were registered at baseline.[27,28] MMSE is a valid test of cognitive function assessing orientation, registration, attention, calculation, recalling, language manipulation, and the ability to follow commands (range: 0−30). A lower score indicates vaster impairment, of which ≤20 is characteristic of dementia.[27]

Statistical Analysis

We described baseline characteristics by frequency, percentage, mean, and standard deviation (SD).

Welch's unequal variance t test was used to compare the change between groups. In line with previous studies, we calculated the total scores without substitution for MMSE, NPI-NH, and CSDD when 80% of questions were answered and performed complete case analysis.[18] The level of significance was p value <0.05. We used multilevel mixed-effect negative binomial regression for modeling the number of prescribed psychotropic drugs over time for the intervention and control group. The analysis was carried out with time and unit as random effects to account for local variations in nursing home units. We performed all analysis with Stata or IC, release 16 (StataCorp LP, College Station, TX).

Ethics

The trial followed the recommendations of the Regional Committees for Medical and Health Ethics and Norwegian legislation concerning the matter of consent. All eligible patients and their next of kin or legal guardian received verbal and written information about the trial. If capable, the patient gave written, informed consent in direct conversation. If not, the next of kin or legal guardian provided presumed consent based on their determination of whether the patient, when he or she was able, would have agreed to participate. The Regional Committees for Medical and Health Ethics approved the trial (2013/1765), and ClinicalTrials.gov (NCT02238652) received the requisition prior to trial start.

RESULTS

Of the 723 nursing home patients enrolled in the COSMOS trial, we included in this study 428 patients not lost at the 4-month follow-up stratified into an intervention (N = 217) and control (N = 211) group (Fig. 1 and Table 1). Participants had a mean age of 86 (SD: 7.6), and 325 (76%) were female. The mean MMSE score was 12 (SD: 7.7), and 274 (64%) had a

TABLE 1. Baseline Characteristics for the Selected Sample of 428 Nursing Home Patients From the COSMOS Trial

	Intervention (N = 217)				Control (N = 211)			
	Mean	(SD)	n	(%)	Mean	(SD)	n	(%)
Demography								
Sex, female			165	(76)			160	(76)
Age	86.28	(7.95)			86.60	(7.21)		
Number of diagnoses	3.98	(3.03)			4.25	(3.37)		
Diagnosis of demented			141	(65)			133	(63)
MMSE	11.45	(7.47)	175	(81)	12.09	(7.93)	155	(73)
Drugs in general								
Total number	10.92	(4.60)	216	(100)	10.90	(4.69)	207	(98)
Regularly	7.49	(3.55)	214	(99)	7.63	(3.75)	207	(98)
On-demand	3.44	(2.28)	204	(94)	3.27	(2.00)	195	(92)
Psychotropic drugs								
Total number	2.18	(1.60)	187	(86)	2.24	(1.65)	175	(83)
Regularly	1.30	(1.19)	154	(71)	1.36	(1.24)	153	(73)
≥1 regularly	1.83	(1.01)	154	(71)	1.87	(1.07)	153	(73)
≥3 regularly	3.55	(0.62)	31	(14)	3.50	(0.77)	36	(17)
Classes regularly prescribed								
Antipsychotic drugs	0.19	(0.45)	37	(17)	0.13	(0.38)	25	(12)
Anxiolytic drugs	0.21	(0.43)	44	(20)	0.25	(0.50)	48	(23)
Hypnotic or sedative drugs	0.28	(0.49)	57	(26)	0.36	(0.55)	69	(33)
Antidepressant drugs	0.46	(0.63)	85	(39)	0.45	(0.58)	86	(41)
Antidementia drugs	0.15	(0.37)	32	(15)	0.16	(0.37)	34	(16)

N: sample; n: number of patients; SD: standard deviation; MMSE: mini-mental status evaluation; range 0−30, a lower score indicates vaster impairment of which ≤20 is characteristic for dementia. Diagnoses per the International Classification of Primary Care (ICPC). All drugs set in a schedule are regarded as regularly prescribed drugs; all other drugs were registered as on-demand. Drugs prescribed regularly plus those on-demand equals the total number of prescribed drugs. Psychotropic drugs: antipsychotics (N05A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D) according to the Anatomical Therapeutic Chemical Index (ATC).

TABLE 2. Secondary Outcome Measures at Baseline for the Selected Sample of 428 Nursing Home Patients From the COSMOS Trial

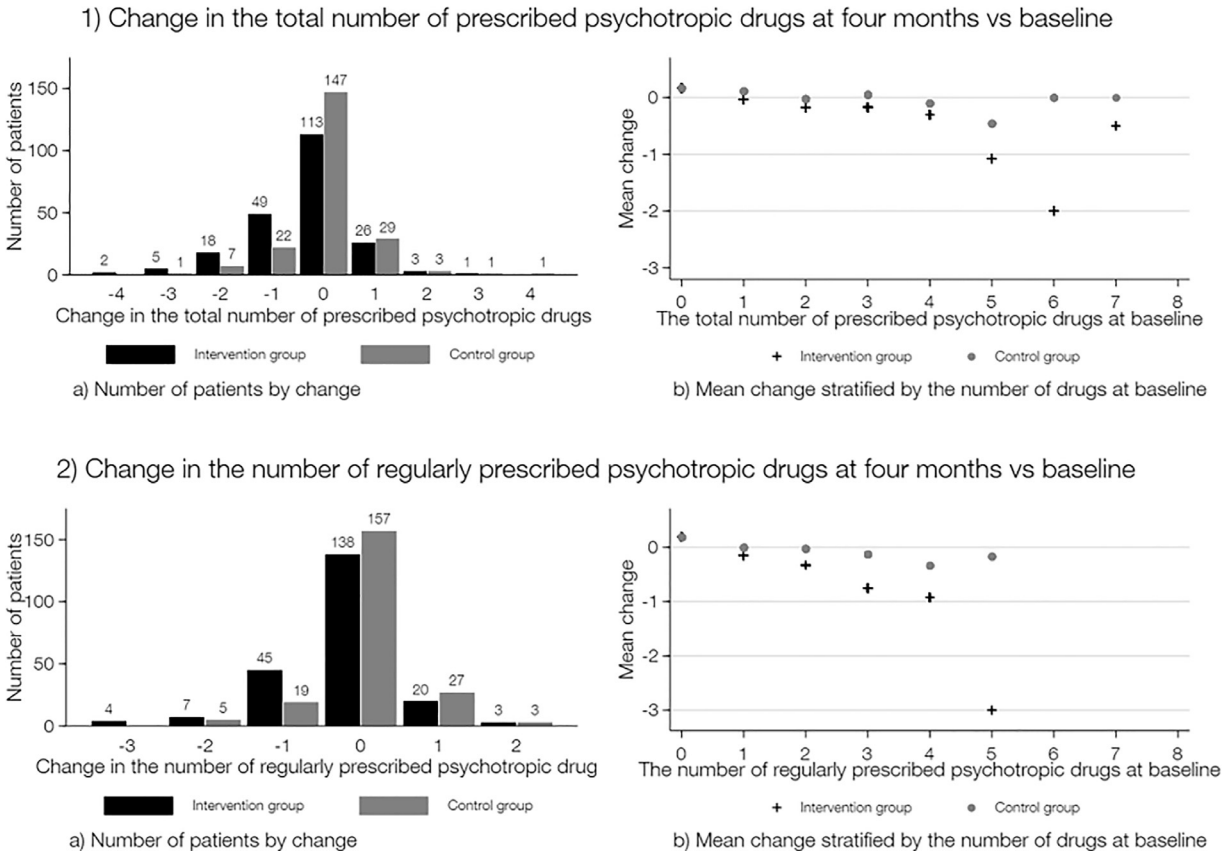
	Intervention (N = 217)			Control (N = 211)		
	Mean	(SD)	n	Mean	(SD)	n
Behavioral and psychological symptoms of dementia						
NPI-NH						
Total score	17.49	(18.97)	215	17.61	(21.12)	204
Domains						
Delusions	1.37	(2.88)	216	1.87	(3.52)	204
Hallucinations	0.69	(2.05)	216	0.86	(2.54)	206
Agitation	2.15	(3.44)	213	1.89	(3.43)	204
Depression	2.49	(3.67)	214	1.80	(3.21)	204
Anxiety	2.20	(3.84)	214	2.35	(3.82)	205
Euphoria	0.35	(1.46)	214	0.39	(1.55)	205
Apathy	1.26	(2.65)	213	1.00	(2.24)	203
Disinhibitions	1.25	(2.79)	216	1.31	(2.84)	204
Irritability	2.57	(3.45)	214	2.77	(3.82)	205
Aberrant motor behavior	0.85	(2.44)	213	1.20	(3.14)	205
Sleep disturbances	1.61	(3.18)	215	1.65	(3.06)	204
Appetite changes	1.26	(2.65)	213	1.00	(2.24)	203
≥1 domain of clinical relevance, n (%)	154	(71)	217	134	(64)	211
CSDD						
Total score	7.30	(6.33)	214	7.56	(6.40)	205
Total score of clinical relevance, n (%)	85	(39)	214	90	(43)	205
Level of functioning						
PSMS total score	17.25	(5.14)	216	16.43	(5.49)	206
Toileting	2.90	(1.57)	216	2.59	(1.47)	206
Feeding	1.71	(1.09)	216	1.70	(1.06)	206
Dressing	3.07	(1.17)	216	2.96	(1.30)	206
Grooming	3.39	(0.97)	216	3.25	(1.11)	206
Physical ambulation	2.79	(0.93)	216	2.77	(0.88)	206
Showering	3.38	(0.98)	216	3.19	(1.02)	205

N: sample; n: number of patients; SD: standard deviation; NPI-NH: 12 item Neuropsychiatric Inventory Nursing Home Version, total scores range 0−144, domain scores range 0−12; scores ≥4 are considered of clinical relevance; CSDD: Cornell Scale of Depression in Dementia, total scores range 0−38, scores ≥8 are considered of clinical relevance; PSMS, Lawton and Brody's Physical Self Maintenance Scale, range 6−30, higher scores indicate a lower level of functioning in activities of daily living.

formal diagnosis of dementia. Three hundred and seven (72%) patients used psychotropic drugs regularly, and 67 (16%) used three or more, while 268 (63%) received psychotropic drugs on-demand. Antidepressants were the most frequent regularly prescribed psychotropic drug (40%; Table 1), while anxiolytics were most often prescribed on-demand (48%, data not shown). Clinically relevant BPSD assessed by NPI-NH were present for 288 (67%) patients, with the highest mean scores occurring in the domains of irritability and anxiety (Table 2). According to the CSDD, 175 (41%) met the criteria for clinical relevant depression (Table 2). The overall mean PSMS score was 17 (SD: 5.3).

From baseline to month 4, 74 (34%) patients in the intervention group discontinued at least one prescribed psychotropic drug, given either regularly or on-demand; the corresponding number was 30 (14%) among those randomized into the control group (Panel 1a, Fig. 2). Similarly, 56 (26%) patients in the intervention group and 24 (11%) in the control group discontinued any regularly prescribed psychotropic drugs (Panel 2a, Fig. 2). Panel 1b and 2b of Figure 2 visualizes the mean changes in psychotropic drug use stratified by the number of prescribed psychotropics in the intervention and control groups. Table 3 quantifies these reductions, showing that the number of discontinued drugs in the intervention group increased by higher numbers of psychotropic drugs at baseline. Patients in the intervention group who were regularly prescribed three or more psychotropic drugs at baseline (n = 31) had a significantly higher mean reduction compared to the control group (n = 36; Table 3). Compared to the control group, the regular use of hypnotics or sedatives (N05C) and antidepressant drugs (N06A) were reduced during the intervention (Table 3), while no difference in mean

FIGURE 2. Changes in prescribed psychotropic drugs at 4 months versus baseline for the selected sample of 428 nursing home patients from the COSMOS trial. Panel 1 illustrates changes in the total number of prescribed psychotropic drugs. Panel 2 illustrates changes in regularly prescribed psychotropic drugs. Mean changes stratified by the number of prescribed psychotropic drugs at baseline; (1b) the total number and (2b) in regular use.



change for antipsychotics (N05A), anxiolytics (N05B), and antidementia drugs (N06D) were found.

The mean change in total NPI-NH score did not differ between the intervention group and the control group, nor did the domain scores or the mean change in the CSDD total score (Table 3). Level of functioning in ADL, measured by the PSMS total score at month 4, improved overall for the intervention group and worsened in the control group, yet none of the discrete items differed (Table 3).

We performed a multilevel mixed-effect negative binomial regression with random effects of time and nursing home clusters and found no association between time and cluster variations regarding prescribed psychotropic drugs by total number or regularly prescription (data not shown). Defining antiepileptic drugs (N03A)[23] as psychotropic drugs increased the number of patients using psychotropic drugs at baseline by three persons, in both the intervention and control group. This led to no alterations in the primary and secondary outcome measures (data not shown). As a measure of adverse events, we conducted a post hoc analysis, showing no differences in hospitalizations between the groups at follow-up (data not shown).

DISCUSSION

Our medication review based on collegial mentoring and systematic clinical evaluation reduced the prescription of psychotropic drugs in nursing home patients without any deterioration in their behavioral

TABLE 3. Changes Within the Intervention and Control Group at 4 Months Versus Baseline for the Selected Sample of 428 Nursing Home Patients From the COSMOS Trial

	Four Months Versus Baseline							
	Intervention (N = 217)			Control (N = 211)				
	Mean	(SD)	n	Mean	(SD)	n	df	p Value*
Drugs in general								
Total number	-1.31	(2.90)	217	-0.31	(1.92)	211	418	<0.001
Regularly	-0.99	(2.32)	217	-0.30	(1.64)	211	418	<0.001
Psychotropic drugs								
Total number	-0.34	(1.01)	217	0.01	(0.77)	211	426	<0.001
Regularly	-0.21	(0.78)	217	0.02	(0.61)	211	426	<0.001
≥1 regularly	-0.37	(0.82)	154	-0.05	(0.65)	153	305	<0.001
≥3 regularly	-0.97	(1.05)	31	-0.17	(0.65)	36	65	<0.001
Classes regularly prescribed								
Antipsychotic drugs	-0.02	(0.33)	217	0.02	(0.23)	211	426	0.087
Anxiolytic drugs	-0.01	(0.33)	217	-0.01	(0.32)	211	426	0.874
Hypnotic or sedative drugs	-0.03	(0.39)	217	0.06	(0.33)	211	426	0.011
Antidepressants drugs	-0.11	(0.46)	217	0.02	(0.36)	211	426	0.041
Antidementia drugs	-0.04	(0.27)	217	-0.02	(0.18)	211	426	0.555
Behavioral and psychological symptoms of demented								
NPI-NH								
Total score	-3.41	(20.63)	212	-0.90	(17.07)	200	410	0.180
Domains								
Delusions	-0.31	(3.28)	213	-0.10	(3.24)	201	412	0.532
Hallucinations	-0.02	(2.21)	215	0.00	(2.32)	203	416	0.899
Agitation	-0.75	(3.49)	212	-0.36	(3.22)	201	411	0.242
Depression	-0.63	(4.10)	209	-0.19	(2.71)	199	406	0.203
Anxiety	-0.23	(3.97)	209	-0.43	(3.49)	201	408	0.592
Euphoria	-0.11	(1.48)	211	0.20	(1.88)	202	411	0.058
Apathy	-0.30	(3.26)	211	0.14	(2.41)	198	407	0.124
Disinhibitions	-0.21	(2.94)	215	0.14	(2.93)	200	413	0.226
Irritability	-0.68	(3.88)	210	-0.31	(3.31)	201	409	0.303
Aberrant motor behavior	-0.08	(2.60)	211	-0.06	(3.37)	202	411	0.943
Sleep disturbances	-0.25	(2.92)	215	-0.25	(2.82)	201	414	0.993
Appetite changes	0.18	(3.28)	212	0.32	(2.18)	198	408	0.615
CSDD								
Total score	-0.18	(6.05)	213	-0.14	(5.66)	202	413	0.945
Level of functioning								
PSMS total score	-0.13	(4.22)	216	0.73	(3.45)	204	418	0.023
Toileting	-0.01	(1.33)	216	0.15	(1.31)	203	417	0.196
Feeding	0.12	(0.95)	216	0.17	(0.76)	203	417	0.501
Dressing	0.01	(1.10)	216	0.20	(0.90)	203	417	0.058
Grooming	-0.04	(1.00)	214	0.13	(0.84)	201	413	0.061
Physical ambulation	0.02	(0.86)	216	0.13	(0.74)	204	418	0.165
Showering	-0.18	(1.12)	216	0.00	(1.06)	203	417	0.091

N: sample; n: number of patients; SD: standard deviation; df: degrees of freedom; NPI-NH: 12 item Neuropsychiatric Inventory Nursing Home Version, total scores range 0–144, domain scores range 0–12; CSDD: Cornell Scale of Depression in Dementia, total score range 0–38; PSMS: Lawton and Brody's Physical Self Maintenance Scale, range 6–30, higher scores indicate a lower level of functioning in activities of daily living.

*Welch's unequal variance t test was used to compare the change between groups. All drugs set in a schedule are regarded as regularly prescribed drugs, all other drugs were registered as on-demand. Adding drugs regularly prescribed drugs to on-demand equals the total number of prescribed drugs. Psychotropic drugs: antipsychotics (N05A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D) according to the Anatomical Therapeutic Chemical Index (ATC).

disturbances. Highest reductions in number of psychotropic drugs were found among patients who received several at baseline. Most frequently, antidepressants and sedatives were reduced, leading to a significant clinical improvement in the patients' physical function. Even though we acknowledge that psychotropic drugs are beneficial for some, our findings emphasize that *less* inappropriate psychotropic drug prescription has the potential for *more* and better physical function in nursing home patients.

We report an overall reduction in use of psychotropic drugs, which did not lead to compensatory increased use of psychotropic drugs on demand. A noncontrolled study conducted psychotropic prescription reviews solely based on medical records in aged care facilities, resulting in a 24% discontinuation of antipsychotic drugs and benzodiazepines.[11] This resembles our finding of a modest reduction in regularly prescribed psychotropic drugs after a 4-month follow-up. However, joint reviews integrating measures of cognitive and physical impairment in a pre- or postintervention trial greatly reduced persistent use of the major classes of psychotropic drugs in institutionalized patients with dementia.[12] We found the highest reductions among patients receiving several psychotropic drugs and those classes of drugs most often prescribed in nursing homes today, namely antidepressants and hypnotics or sedatives.[3] The major attention given to the possible overuse of, in particular, antipsychotic medication in nursing homes the last decade in many ways paved the way for the development of the COSMOS intervention.[3,29] As such, relatively few patients used these drugs at baseline (Table 1), partly explaining the lack of significant reductions in use of antipsychotic medication.

This is the first RCT that reports on BPSD concerning the process of deprescribing more than two classes of psychotropic drugs in a nursing home sample. Despite reductions in overall psychotropic drug use, we found no emerging difference in BPSD between the intervention and control group, supported by previous reports indicating that separate classes of psychotropic drugs can be safely withdrawn if done cautiously.[15,30] In several cohorts, multi-psychotropic drug use was associated with severe BPSD, illustrating the symptom complexity and therapeutic shortcomings of available medication.[3] The highly remitting and relapsing course of BPSD further complicates interpretations of the cause and effects of these drugs, whose side effects such as latency, apathy, and anxiety might also mimic BPSD.[2,7,31] The randomized CATIE-AD trial found similar symptom-trajectories of BPSD, irrespective of treatment with second-generation antipsychotic drugs among 371 patients with Alzheimer's dementia.[32] The retrospective reporting from the HALT study found that antipsychotic medication were prescribed as a maintenance treatment, despite absence of BPSD, and that standardized medication review alone were insufficient to withdraw prolonged administration of antipsychotics in long-term care.[10] However, the DESEP trial induced exacerbating depressive symptoms following an intervention exclusively comprising randomized discontinuation of antidepressants for nursing home patients with BPSD and dementia.[9] In contrast, the WHELD trial randomized nursing home patients into antipsychotic review alone or in combination with social and physical exercise.[5] The results showed that BPSD increased in the group that only received medication reviews, underlining the importance of nonpharmacological interventions implemented alongside medication reviews. In our trial, all the additional COSMOS components − communication and advanced care planning, pain management, activities, and focus on safety − likely contributed to the stabilization of BPSD following medication reviews.[2,5,15] Differing designs and populations obviously challenge direct comparisons of interventions solely reviewing medication contrasting those additionally including nonpharmacological elements. Nonetheless, these reports consolidate the COSMOS strategy for individualized care by incorporating assessments of BPSD and identifying both underlying medical issues and unmet needs in combination with nonpharmacological approaches, balancing the twin traps of overtreatment and therapeutic nihilism in nursing home medicine.[2,30,33,34]

During this 4-month study, the patients in the intervention group improved in ADL, whereas the dependency of the control group was aggravated. Our findings are encouraging, as the loss of ADL skills in dementia are regarded as irreversible.[35] A range of factors including progression of cognitive impairment, BPSD, and psychotropic drugs condition the loss of ADL skills, likely increasing the risk of exacerbating BPSD.[8,31,35] This can, in a worst case scenario, initiate a self-enforcing circle of accumulating and lingering psychotropic drug therapy, again aggravating dependence in ADL.[3,8,10] Few studies have explored the association between pharmacological treatment of BPSD and ADL. Some have found advantageous effects, particular concerning the use of antidepressants, although it is debated whether this effect is of clinical relevance.[36,37] Anxiolytic drugs, however, substantially impaired ADL, despite improvement in BPSD among 89 patients with dementia admitted to acute psychogeriatric inpatient wards.[38] Further, antipsychotics, in addition to

anxiolytics, were associated with functional decline in ADL for 236 home-dwelling elderly with dementia.[39] Interestingly, Global Assessment of Functioning score improved by electroconvulsive treatment in agitated elderly patients with dementia, while both BPSD and psychotropic drug use decreased.[40] Nevertheless, being a tool for overall assessment of functioning, the Global Assessment of Functioning score describes how well the patient meets various problems-in-living and does not equate to ADL per se. That being said, their findings corroborate a more dynamic understanding of ADL in dementia as reversible through both pharmacological and nonpharmacological interventions.

A principal strength of the COSMOS trial is the rigorous method for comprehensive medication review with a multidisciplinary, systematic approach that utilizes validated assessments.[16] Physicians working in municipal nursing homes, the majority being general practitioners, were recruited to the trial and placed in charge of undertaking the medication reviews and further treatment. This suggests that the method can be adapted in other first-line clinical settings, not determinant on specialist qualifications. Further, the COSMOS trial is the largest RCT conducted in an unselected sample of nursing home patients, yielding high generalizability of our findings. The large sample size allowed for the investigation of several classes of psychotropic drugs prescribed regularly and on-demand, including their associations with clinically relevant outcomes, such as BPSD and physical functioning.

Our findings should be interpreted in light of some limitations. This was a completers only analysis limiting the generalizability to nondeceased patients. Some of the physicians responsible for the systematic medication reviews worked in both the intervention and control units. Therefore, the principles for medication reviews could have contaminated the outcomes of the control group, possibly reducing the difference in change in psychotropic drugs between our two comparison groups. We also expect a reduced intervention effect caused by treatment that was started during admission to hospital or prescribed by external physicians not familiar with the COSMOS trial, as indications and durations of therapy were not registered. Some aspects of the COSMOS intervention are likely less feasible in clinical practice, due to resource demanding nonpharmacological components and logistics, such as researchers mentoring the nursing home physicians in performing medication reviews.[16] Due to multiple testing, the chance of false-positive findings increase. Further, we did not consider defined daily doses of the various classes of psychotropic drugs, nor other influencing factors on BPSD such as pain assessments and analgesics. As data on BPSD and ADL had to be assessed by the caregivers most proximate to the patients being the once also delivering the intervention, the single-blinded design can increase the risk of reporting bias.

CONCLUSION

Medication review with collegial mentoring based on systematic clinical evaluation reduced the prescription of psychotropic drugs in nursing home patients without deterioration in BPSD, yet independence in ADL improved. This illustrates that less is actually more concerning psychotropic drug use and overall functioning. Our procedure represents valuable decision-making support for the clinician to establish and maintain appropriate psychotropic prescribing in nursing homes.

AUTHOR CONTRIBUTIONS

MHG led the conception of work and analyses, as well as the interpretation of data for publication and the writing of the manuscript. LIB, BSH, JM, MN, and RLSK contributed to the design and the writing of the manuscript, namely preparation and critical revision. JM supervised the analyses. BSH was primary investigator for the COSMOS trial. All authors have read and approved the final version for publication.

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DISCLOSURE

The authors report no conflicts with any product mentioned or concepts discussed in this article.

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