Scoping Review of Randomized Trials With Discontinuation of Medicines in Older Adults

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A B S T R A C T

Objectives: To map the randomized trial evidence describing the feasibility of discontinuing active medications with potential adverse effects in older patients.

Design: Scoping review with systematic search of PubMed, Embase, and Cochrane Library.

Setting and Participants: Randomized trials investigating discontinuation of a single medicine or medicine class in patients with mean age ≥65 years.

Methods: We extracted trial characteristics including study design and assessed bias. As proxies for the "feasibility of discontinuation," we extracted the "dropout rate" and "disease recurrence rate.

Results: We identified 40 trials investigating discontinuation of symptomatic (n = 26), preventive (n = 6), or both preventive and symptomatic medicines (n = 8) against psychiatric (n = 10), neurologic (n = 9), musculoskeletal (n = 8), cardiovascular (n = 5), respiratory (n = 4), and urologic diseases (n = 4). Five discontinuation designs were used, 75% (30/40) of trials were placebo-controlled, and 48% (19/40) of trials had bias disfavoring discontinuation. The dropout rate was similar between the discontinuation group and the continuation group in 79% of the trials (30/38), whereas disease recurrence was similar in 72% (23/32) of the trials. In 42% (13/31) of trials reporting both dropout rate and disease recurrence rate, the differences between groups were statistically insignificant and less than 10%; these trials investigated discontinuation of cholinesterase inhibitors for Alzheimer's disease in various settings (n = 3), alendronate for osteoporosis (n = 3), glucosamine for osteoarthritis, lithium as adjunct for unipolar depression, statins for cardiovascular disease in patients with limited life expectancy, droxidopa for neurogenic orthostatic hypotension, tamsulosin for lower urinary tract symptoms, sertraline for major depressive episode, and fentanyl patch for low back or osteoarthritis pain.

Conclusions and Implications: We identified 40 randomized trials using a variety of designs investigating discontinuation of both symptomatic and preventive medicines in older patients. Discontinuation of medicines seems feasible for most of the investigated medicines. This scoping review can guide clinical practice and future trials on deprescribing.

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Health care services throughout the world are faced with increasing challenges because of multimorbidity and polypharmacy. The prevalence of chronic diagnoses increases with age, and consequently older adults are increasingly exposed to polypharmacy. As all medications carry a risk of adverse drug reactions, polypharmacy is associated with an increased risk of adverse drug reactions but also with increased risk of inappropriate medicine use and adverse health outcomes in general. To deprescribe inappropriate medicines (ie, reducing the use of...
medicines with a negative risk-benefit profile in a particular patient), it is necessary to know which medicines can be safely continued or discontinued. Unfortunately, few randomized controlled trials investigate the efficacy and safety of medicines in older adults and even fewer trials investigate the effect of discontinuing medicines in older adults. The objective of this scoping review is to map the “evidence-landscape” of medication discontinuation in older patients. We aim to provide an overview of the existing randomized controlled trials and, based on the evidence, describe the feasibility of discontinuation of investigated medicines in older patients.

Methods
This article is structured according to the PRISMA extension for Scoping Reviews (PRISMA-ScR) (Supplementary Material 1). There is no published protocol for this review.

Information Sources and Search Strategy
We systematically searched PubMed (coverage 1966 to present), Embase (coverage 1947 to present), and the Cochrane Library (coverage 1992 to present) for publications on randomized discontinuation trials in older patients defined as patients aged ≥65 years. The search was last updated on the 11th of June 2021. The search strings are available in Supplementary Material 2.

Selection of Sources of Evidence
All references were imported into Covidence, where 2 authors (J.K. and C.B./A.M.S.S.) independently screened abstracts and full texts and included studies according to the eligibility criteria. Consensus was reached through discussion or through judgment of a third author (M.B.C.).

The eligibility criteria were as follows:

- Randomized controlled trials investigating the discontinuation of a single medicine or a single medicine class, where medicine class was defined as medicines having a similar pharmacologic effect as judged by the authors
- Mean age ≥ 65 years in total or in 1 or more arms

The exclusion criteria were as follows:

- No randomized discontinuation intervention
- Full text not in English
- More than 1 medicine or medicine class discontinued
- Discontinued medicines targeting cancer, transplant complications, or infections, because these treatments are highly specialized or of limited duration
- Not published as full-length, peer-reviewed manuscript (eg, poster publications or clinical trial registrations)
- Temporary discontinuation, that is, pausing of medicines

We limited the studies to discontinuation of a single medicine or a single medicine class with similar pharmacologic effect for ease of interpretability. As an example, antihypertensives cover a diverse range of pharmacologic effects and the choice of antihypertensive medicine for older patients may be influenced by the patient’s comorbidities, other concurrent medication, frailty and fall risk, which makes generalizing the feasibility of discontinuation of such a medicine class difficult.

Data Charting Process
Data were extracted to a customized Google Sheet, and aggregated with the tidyverse package in R via RStudio. Figures were produced using ggplot2 and plotly in R.

Data Items
The extracted data items included author, publication year, number of patients, discontinued medicine or medicine class, population, setting and treatment indication, study design including blinding, “feasibility of discontinuation,” other relevant results such as particular treatment-related efficacy/harms, and comments (eg, limitations to the study).

To describe the “feasibility of discontinuation,” we extracted 2 measures: (1) the “dropout” rate defined as the proportion of patients who did not complete the entire study per protocol in the discontinuation and continuation groups; and (2) the “disease recurrence” rate defined as the proportion of patients with disease appearance for preventive treatments (eg, fractures after discontinuation of bisphosphonate treatment) or clinical worsening of the treated disease only for primarily symptomatic treatments (eg, pain after opioid treatment withdrawal) in the discontinuation and continuation group. Although adverse drug withdrawal events (ADWES) can be due to either disease recurrence or physiological reactions to the discontinuation of medicines, this measure focused on disease recurrence as the dropout rate should capture serious ADWES due to physiological reactions. Thus, if beta-blockers are used to treat congestive heart failure and a patient experiences worsening in heart failure, then it would be considered disease recurrence. In contrast, if the patient experiences tachycardia then it is not, but it may be captured in the dropout rate if the patient exits the study because of the ADWE. To identify disease recurrence, we categorized treatment as primarily “symptomatic” if used to alleviate symptoms present (eg, fentanyl for pain), “preventive” if primarily used to prevent future events in a condition that is asymptomatic (eg, statins for prevention of cardiovascular events), or both “symptomatic and preventive” (eg, selective serotonin reuptake inhibitors for depression) as judged by the authors. We defined a difference as less than 10% in both dropout and disease recurrence rate as “small.” For trials with more treatment groups than just randomized discontinuation and continuation, we only extracted and present data from the randomized discontinuation and continuation groups.

Critical Appraisal of Evidence
Existing risk of bias evaluation tools were not suitable in their entirety. We used the first domain from Cochrane Risk of Bias tool to assess the risk of bias arising from the randomization process. In addition, we assessed the comparator bias that could lead to a differential dropout rate by answering the following 4 questions: (1) Were the discontinued medicine(s) primarily symptomatic, preventive or both? Our hypothesis was that symptomatic treatments are more prone to differential dropout rates because of poor blinding. (2) Was tapering needed and if so, was the tapering strategy adequate to avoid withdrawal symptoms? (3) Was the study adequately blinded? and (4) Any other design choices which may result in differential dropout rates? Two authors (J.K. and A.M.S.S.) independently answered these questions for each trial and assessed the risk of bias as “low risk,” “some concern,” or “high risk.” In general, nonblinded studies were classified as high risk for symptomatic medicines and some concern for preventive medicines, studies with inadequate tapering were high risk, and studies where tapering was needed and mentioned, but not described in detail, were classified as some
concern. Consensus was reached through discussion or via the judgment of a third author (M.B.C.).

**Synthesis of the Results**

To identify disease areas and medicines where discontinuation trials exist, we aggregated the data on medical specialty, indication for the treatment, and the medicine(s) discontinued. To provide an overview of the feasibility of discontinuation of the individual medicines, we plotted the dropout rates and disease recurrence rates in the discontinuation and continuation group, the size of the studies, and the risk of bias. To identify treatment areas where discontinuation may not be feasible, we compared the difference between the discontinuation and the continuation group for both the dropout and disease recurrence rate. A priori, the dropout and disease recurrence rates were expected to be greater in the discontinuation group compared with the continuation group. Therefore, the differences in these rates were compared using a 1-sided Fisher exact test in R version 3.6.3, and a 1-sided \( P < .05 \) was considered statistically significant. To identify treatment areas where discontinuation may be feasible, we extracted the trials where the above-mentioned differences were both statistically insignificant and where the absolute difference between groups for both rates was less than or equal to 10%, corresponding to a number to discontinue of 10 for 1 additional dropout and/or 1 additional disease recurrence. Other relevant outcomes could not be readily synthesized and are presented narratively or in tables.

**Results**

**Selection of Studies**

In total, we screened 3304 records and included 41 publications comprising 40 unique trials. See Figure 1 for study selection.

**Characteristics of Sources of Evidence**

An overview of the included trials is presented in Figure 2, where the medical specialty, indication for the treatment, and the discontinued medicine(s) are visualized. Additional information on the included trials is available in Supplementary Table 1. Of the included trials, 65% (26/40) of the discontinued medicines were primarily symptomatic, 15% (6/40) were primarily preventive, and 20% (8/40) were both preventive and symptomatic. The setting of the patient recruitment was outpatient clinics (20/40 = 50%); nursing homes (5/40 = 12.5%); the community, for example, using advertisements (5/40 = 12.5%); general practitioners (4/10 = 10%); unknown, that is, multicenter studies with no description of the setting (4/40 = 10%); hospital admissions (1/40 = 2.5%); and palliative care (1/40 = 2.5%).

The designs of the 40 included trials are presented in Figure 3 (designs A-E) along with the designs of the 64 excluded trials (designs F-J). Most of the included trials (20/40 = 50%) randomized patients already on the study medicine (design A), 10% (4/40) were an extension to a parent trial with randomized discontinuation for patients on the study medicine (design B), 15% (6/40) were randomized discontinuation of 1 medicine after combination therapy with 2 medicines (design C), 23% (9/40) were randomized discontinuation of the study medicine for patients with initial effect of the study medicine (design D), and 1 trial (3%) was a crossover trial for patients already on the study medicine (design E). Of the included trials, 25% (10/40) were nonblinded and 75% (30/40) were placebo-controlled.

**Critical Appraisal of Sources of Evidence**

The bias assessments are presented in Supplementary Table 2. In summary, 5% of the trials (2/40) had high risk of bias regarding randomization whereas 45% (18/35) had “some concern” (most of them due to an inadequate description of the randomization process). Regarding differential dropout rates, 48% (19/40) of the trials had bias disfavoring the discontinuation group. Of these 19 trials, 53% (10/19)
had high risk of bias, while 47% (9/19) had “some concern.” There was low risk of bias across both domains in 25% of the trials (10/40).

**Results and Synthesis of Results of Sources of Evidence**

**Dropout rate**

The dropout rate in the discontinuation group compared with the continuation group is presented in Figure 4 for all the included trials, except for 2 trials where this information was not reported. The dropout rate varied from 0% in both groups to a maximum of 83% in the discontinuation group and 70% in the continuation group. The difference in dropout rates was statistically significantly greater in the discontinuation group compared with the continuation group in 21% of the trials (8/38). These 8 trials investigated discontinuation of amantadine for levodopa-induced dyskinesia in Parkinson’s disease, donepezil for dementia due to Alzheimer’s disease, citalopram for unipolar major depressive episode, fentanyl patch for pain due to postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain, fluticasone propionate for chronic obstructive pulmonary disease.
Fig. 3. Overview of study designs containing an element of medicine discontinuation. The number of arms can vary and are not limited to those visualized in the figure. The discontinuation can be blinded (ie, continued placebo treatment) or nonblinded (no medicine taken in the discontinuation group).
pulmonary disease, risperidone for psychosis or agitation-aggression due to Alzheimer’s disease, beta-blockers for heart failure after cardiac resynchronization therapy, and galantamine for dementia due to Alzheimer’s disease. Of these 8 trials, 3 trials had a high risk of bias for differential dropout rates because of inadequate tapering of amantadine or citalopram or due to nonblinded discontinuation of beta-blockers with more planned study visits in the discontinuation group.

Disease Recurrence Rate

The disease recurrence rate was reported in 80% (32/40) of the included trials, and disease recurrence in the discontinuation group compared with the continuation group is presented in Figure 5. The disease recurrence rate varied from 0% in both groups to a maximum of 80% in the discontinuation group and 70% in the continuation group. The difference in disease recurrence rates was statistically significantly greater in the discontinuation group compared with the continuation group in 28% of the trials (9/32). Of these 9 trials, 5 trials also had greater dropout rates in the discontinuation groups and were described above, that is, amantadine, risperidone, fentanyl patch, citalopram, and fluticasone propionate. The remaining 4 trials not previously described investigated discontinuation of tamsulosin for lower urinary tract syndrome, citalopram or sertraline for patients living in nursing homes without a history of depression, SSRIs for neuropsychiatric symptoms due to dementia, and nitrates for angina pectoris. Of the 9 trials, 3 trials had a high risk of bias because of inadequate tapering of SSRIs, amantadine, or nonblinded discontinuation of nitrates.

Dropout and Disease Recurrence Rate

In total, 31 trials reported both dropout rates and disease recurrence rates. In 13 of these 31 trials, the difference in both dropout rate and disease recurrence rate were statistically insignificant and less than 10% for the discontinuation group compared with the continuation group. These 13 trials investigated discontinuation of glucosamine for osteoarthritis and mild to moderate dementia due to Alzheimer’s disease and with uncertain clinical benefit of the treatment, lithium as adjunct to treatment for unipolar depression, alendronate for osteoporosis, statins as primary or secondary prevention of cardiovascular disease in patients with limited life expectancy, droxidopa for neurogenic orthostatic hypotension, tamsulosin for lower urinary tract symptoms, donepezil for dementia and neuropsychiatric symptoms due to Alzheimer’s disease, sertraline for patients with major depressive episode, clonazepam for dementia due to Alzheimer’s disease in patients living in nursing homes.
and fentanyl patch for low back pain or pain due to osteoarthritis.31

**Discussion**

**Findings**

We identified 40 unique discontinuation trials with inclusion of older patients. Of these trials, 12 trials had dropout rates and/or disease recurrence rates that were statistically significantly higher in the discontinuation group compared with the continuation group, suggesting that discontinuation may not be feasible for these medicines in these populations. Further, we identified 13 trials where the difference in both dropout rates and disease recurrence rates were small (≤10%) and statistically insignificant, suggesting that discontinuation may be feasible. Interestingly, one study investigating discontinuation of nitrates for angina pectoris in stable patients19 resulted in a statistically significantly higher risk of disease recurrence (8/80 = 10\% vs 0/40 = 0\%), but with an absolute difference in disease recurrence of 10\%. This highlights the complexity of the interpretation of these studies where statistical significance does not always equate clinically relevant differences and underlines why the results presented in this review must be interpreted in the context of the diseases studied. In addition, this example shows that for some of the therapeutic areas where there was a statistically significant difference in dropout rate or disease recurrence, discontinuation attempts may still be feasible in clinical practice, that is, in this study 90\% of the attempts were successful and the few disease recurrences were successfully treated with reinstated therapy.

Another complexity highlighted in the present review is the relatively high proportion of patients with disease recurrence in certain therapeutic areas, also in continuation groups (Figure 5); for example, 41\% (13/32) of the trials reported disease recurrence rates ≥20\% in both groups. A high baseline recurrence risk complicates discontinuation in clinical practice because patients may experience disease recurrence during discontinuation attempts that may in fact be unrelated to the discontinuation attempt, but this is in practice impossible to know and may lead to reinitiation of treatment. This underlines the importance of randomized discontinuation trials as the baseline risk of disease recurrence cannot be estimated from single-arm discontinuation trials.

**Diseases Where Discontinuation Trials Are Lacking**

The identified discontinuation trials covered many of the most prevalent diseases in older patients.60 However, of the most...
commonly used medicines in older adults,\textsuperscript{61} discontinuation trials were lacking for proton pump inhibitors and platelet inhibitors. Trials on discontinuation of treatment for common diseases such as type 2 diabetes and cardiovascular diseases such as atrial fibrillation were also lacking. In general, trials with discontinuation of purely preventive treatments were not very common (6/40 = 15%). We identified 5 trials with discontinuation of bisphosphonates for the treatment of osteoporosis (5/6 = 83%)\textsuperscript{37–40} and only 1 trial investigating the effect of discontinuing statins for patients at the end of life.\textsuperscript{22} This is probably due to the difficulty of conducting these trials as they require a long follow-up period. Trials with discontinuation of purely symptomatic medicines are simpler to conduct. Here, any recurrence of symptoms should be reversible with reinstated treatment of the discontinued medicines. It is therefore remarkable that we only identified 2 studies\textsuperscript{41,42} with discontinuation trials of medicines for the treatment of pain because analgesics are among the most commonly used medicines for older citizens.\textsuperscript{51} Further studies regarding discontinuation of analgesics in older patients seem warranted.

Considerations for Discontinuation Trial Design

As expected, the included trials were clinically and methodologically diverse with regard to therapeutic area, setting, study design, sample size, reporting of dropouts, harms, and risk of bias. Recently, the need to standardize and optimize the reporting of results from discontinuation trials was highlighted.\textsuperscript{62}

Based on this scoping review, identified trials can be divided into 10 different trial designs with an element of discontinuation (Figure 3). The numerous different designs of the included trials are a challenge for the external validity and renders it almost impossible to summarize and meta-analyze the findings. The design that most resembles the clinical situation is where patients are already receiving a given medicine (design A without a run-in period; Figure 3) or a combination of medicines (design C without a run-in period; Figure 3), but changes in prescription patterns over time (eg, new guidelines) or differences in prescription patterns across geographical regions (eg, countries) can limit the external validity of the findings, because the success of discontinuation will depend on how good those who have prescribed the medicine have been to prescribe to the right patients. Compared to these designs, trials where the medicine is started as part of the discontinuation trial (design A and C with a run-in period or design B; Figure 3) may have a more precisely defined population, but also a higher concentration of responders and are thereby more prone to showing lower feasibility of discontinuation. This feature is exacerbated in trials that only include patients who, in the short term, both tolerate the medicine and have apparent effect of the medicine (design D; Figure 3). Lastly, crossover trials with discontinuation (design E; Figure 3) may have problems with carryover effect and the high dropout rate in many discontinuation trials is problematic when analyzing data from these trials.

Our risk of bias assessment revealed that adequate tapering, blinding, and randomization are key when designing future discontinuation studies, and that high dropout rates seem unavoidable even in studies with low risk of bias; for example, overall 45% (17/38) had dropout rates ≥20% in both groups (Figure 4). Therefore, study outcomes that are less affected by high dropout rates should be considered such as time-to-event analyses as seen in Arai et al.\textsuperscript{31}

Strengths and Limitations

Limitations to this study include the exclusion of trials with patients with a mean age <65 years and the exclusion of trials investigating discontinuation of more than 1 medicine. Another limitation is that the proxies for feasibility of discontinuation we used, that is, disease recurrence rate and dropout rate, only imperfectly describe the feasibility of discontinuation. Disease recurrence, although easy to interpret, is not reported by all trials, and will generally favor continuation because no treatment-related harms (eg, adverse effects) are captured. In contrast, the dropout rate is more difficult to interpret, but this measure is reported univariately and should reflect a conservative estimate of the proportion of patients, where discontinuation is not feasible in clinical practice. As an example of the sometimes conflicting and complementary information these measures convey, a trial with discontinuation of beta-blockers for heart failure in patients with normalized ejection fraction following cardiac resynchronization therapy reported a similar low disease recurrence rate in the continuation and discontinuation groups, but a much higher dropout rate in the discontinuation group (because of withdrawal tachycardia).\textsuperscript{24} Thus, although a combination of the 2 measures provide some reassurance for the feasibility of discontinuation, a good measure of the feasibility of discontinuation is lacking.

Conclusions and Implications

We identified 40 trials with randomized discontinuation of single medicines or similar medicines in older adults. Based on disease recurrence and trial dropout rates, 13 trials were in therapeutic areas where discontinuation of medicines on average are feasible, and 12 trials were in therapeutic areas where discontinuation may not be feasible. The trials were clinically and methodologically diverse in terms of design, therapeutic areas, and reporting of outcomes and harms. Identified therapeutic areas lacking discontinuation trials in older adults include type 2 diabetes and atrial fibrillation. The identified randomized trial evidence may guide deprescribing in clinical practice as well as future clinical trials to avoid overtreatment of older patients.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2022.06.010.

References

Supplementary Material 1.

Search strings

Search string Embase:
1. deprescriptions/
2. (inappropriat* or unnecessar* or discontinu* or deprescrib* or deprescrip* or withdraw* or stop* or cessation).ti.
3. 1 or 2
4. exp Aged/
5. (elder* or “65” or frail or geriatric*).ti,ab,kw,kf.
6. (“nursing home” or “long-term care” or “residential aged care” or “skilled nursing facility” or “aged care facility” or “aged care facilities”).ti,ab,kw.
7. nursing home/
8. 4 or 5 or 6 or 7
9. random*.ti,ab,kw.
10. 3 and 8 and 9

Search string PubMed:
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2. (inappropriat*[Title] OR unnecessar*[Title] OR discontinu*[Title] OR deprescrib*[Title] OR deprescrip*[Title] OR withdraw*[Title] OR stop*[Title] OR cessation[Title])
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7. “Nursing Homes”[Mesh]
8. (#4 OR #5 OR #6 OR #7)
9. random*[Title/Abstract]
10. (#3 AND #8 AND #9)

Search string Cochrane Library:
1. MeSH descriptor: [Deprescriptions] explode all trees
2. inappropriat* or unnecessar* or discontinu* or deprescrib* or deprescrip* or withdraw* or stop* or cessation:ti (Word variations have been searched)
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4. MeSH descriptor: [Aged] explode all trees
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<th>Author (Year)</th>
<th>Medicine Discontinued</th>
<th>Indication</th>
<th>Population</th>
<th>Design (See Figure 3)</th>
<th>Follow-Up Duration</th>
<th>Dropsouts</th>
<th>Disease Recurrence</th>
<th>Other Relevant Results and Comments</th>
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<tr>
<td>George et al (2003)</td>
<td>Nitrates</td>
<td>Symptomatic treatment of angina pectoris</td>
<td>120 nitrate-treated patients without angina or heart failure who were hemodynamically stable for the last 3 mo</td>
<td>Design A. Unblinded without a run-in period and with 2:1 discontinuation</td>
<td>3 mo</td>
<td>Discontinuation: 8/80 = 10% Continued: 0/40 = 0%</td>
<td>Discontinuation: 8/80 = 10% Continued: 1/40 = 2.5%</td>
<td>All subjects with angina after discontinuation experienced symptoms within the first month</td>
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<td>van Kraaij et al (1999) and van Kraaij et al (2000)</td>
<td>Furosemide</td>
<td>Symptomatic treatment of heart failure with preserved ejection fraction (HFpEF)</td>
<td>32 furosemide-treated patients with a history of HFpEF and left ventricular ejection fraction &gt;40%</td>
<td>Design A. Blinded without a run-in period and with 2:1 discontinuation</td>
<td>3 mo</td>
<td>Discontinuation: 5/21 = 24% Continued: 1/11 = 9%</td>
<td>Discontinuation: 2/21 = 10% Continued: 1/11 = 9%</td>
<td>There were no significant differences regarding heart failure score, blood pressure, heart rate, spirometry values, or functional status scores (per-protocol analysis) Total quality of life was better for the group discontinuing statin therapy (mean McGill QOL score, 7.11 vs 6.85; ( P = .04 ))</td>
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<td>Kutner et al (2015)</td>
<td>Statins</td>
<td>Primary or secondary prevention of cardiovascular disease, and no recent active cardiovascular disease</td>
<td>381 adults with advanced, life-limiting illness with an estimated life expectancy of between 1 mo and 1 y and recent deterioration in functional status taking statins for 3 mo or more</td>
<td>Design A. Unblinded without a run-in period and with 1:1 discontinuation</td>
<td>1 y</td>
<td>Discontinuation: 94/189 = 50% Continued: 101/192 = 53%</td>
<td>Discontinuation: 13/189 = 7% Continued: 11/192 = 6%</td>
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<td>Sheppard et al (2021)</td>
<td>Antihypertensives</td>
<td>Symptomatic and preventive treatment of hypertension</td>
<td>569 patients aged ( \geq 80 ) y with controlled systolic blood pressure, receiving ( \geq 2 ) antihypertensive medications</td>
<td>Design C. Unblinded with 1:1 discontinuation. Post hoc subgroup analyses</td>
<td>12 wk</td>
<td>Not reported per medicine</td>
<td>Not reported per medicine</td>
<td>Post hoc analyses and details of dropout and disease recurrence are not reported per medicine</td>
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<td>Nijst et al (2020)</td>
<td>Beta-blockers</td>
<td>Symptomatic and preventive treatment of heart failure</td>
<td>40 patients with heart failure with normalized ejection fractions after cardiac resynchronization therapy (CRT) and no symptoms of heart failure for the past 6 mo on optimal pharmacologic therapy</td>
<td>Design A. Part of 2 ( \times 2 ) design with discontinuation of RAAS and/or beta blockers. Unblinded with 1:1 discontinuation. Only discontinuation of beta-blockers is eligible for inclusion in this review</td>
<td>24 mo</td>
<td>Discontinuation: 12/20 = 60% Continued: 4/20 = 20%</td>
<td>Discontinuation: 1/20 = 5% Continued: 2/20 = 10%</td>
<td>Prompt reinitiation of therapy led to recovery of ejection fraction in 100% of subjects within 6 mo. 58% (7/12) dropouts in the discontinuation group were due to tachycardia</td>
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J. Kornholt et al. / JAMDA 23 (2022) 1926.e11–1926.e35
<table>
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<tr>
<th>Study (Year)</th>
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<th>Continuation</th>
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<tr>
<td>Greenspan et al (2002)</td>
<td>Alendronate</td>
<td>Preventive treatment of fractures</td>
<td>85 women who had completed 2 y of treatment with alendronate and conjugated estrogen in the parent trial. Patients in the parent trial were hysterectomized postmenopausal women with lumbar BMD T score &lt; -1.65.</td>
<td>1 y</td>
<td>Discontinuation: 6/41 = 15%</td>
<td>Continuation: 7/44 = 16%</td>
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<td>Michalská et al (2006)</td>
<td>Alendronate</td>
<td>Preventive treatment of fractures</td>
<td>66 women with postmenopausal osteoporosis and at least 3 y of treatment with alendronate</td>
<td>2 y</td>
<td>Discontinuation: 0/33 = 0%</td>
<td>Continuation: 0/33 = 0%</td>
<td>Discontinuation: 2/33 = 6%</td>
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<td>Black et al (2006)</td>
<td>Alendronate</td>
<td>Preventive treatment of fractures</td>
<td>1099 patients with total hip bone mineral density (BMD) T score &gt; -3.5 and without declining BMD during at least 3 y of treatment with alendronate in the parent trial. Patients in the parent trial were postmenopausal women aged 55-80 y with femoral neck BMD T score &lt; -1.65</td>
<td>5 y</td>
<td>Discontinuation: 36/437 = 8%</td>
<td>Continuation: 68/662 = 10%</td>
<td>Discontinuation: 93/437 = 21%</td>
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<td>Wright et al (2017)</td>
<td>Alendronate</td>
<td>Preventive treatment of fractures</td>
<td>27 women older than 65 y with at least 3 y of treatment with alendronate</td>
<td>6 mo</td>
<td>Discontinuation: 2/14 = 14%</td>
<td>Continuation: 4/13 = 31%</td>
<td>Discontinuation: 0/14 = 0%</td>
</tr>
<tr>
<td>Black et al (2012)</td>
<td>Zoledronic acid</td>
<td>Preventive treatment of fractures</td>
<td>1233 women who had completed 3 y of treatment in the parent trial. Patients in the parent trial were women aged &gt;65 y with BMD T score &lt; -2.5 or T score &lt; -1.5 with osteoporotic vertebral fractures</td>
<td>3 y</td>
<td>Discontinuation: 146/616 = 24%</td>
<td>Continuation: 165/613 = 27%</td>
<td>Not reported</td>
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</tbody>
</table>

Pilot study and mostly administrative outcome measures were reported. BMD increased in the continuation group and decreased in the discontinuation group; the mean difference in change ranged from 1.04% to 2.03% depending on site (max P = .002). There was no statistically significant difference in incidence of clinical fractures at any site. (continued on next page)
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Medicine Discontinued</th>
<th>Indication</th>
<th>Population</th>
<th>Design (See Figure 3)</th>
<th>Follow-Up Duration</th>
<th>Dropouts</th>
<th>Disease Recurrence</th>
<th>Other Relevant Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cibere et al (2004)</td>
<td>Glucosamine</td>
<td>Symptomatic treatment of pain</td>
<td>137 patients with pain due to osteoarthritis who were not taking any opioid analgesics and had improvement in pain after at least 1 month of treatment with glucosamine</td>
<td>Design A. Blinded without a run-in period and with 1:1 discontinuation</td>
<td>24 wk</td>
<td>Discontinuation: 0/66 = 0% Continuation: 3/71 = 4%</td>
<td>Discontinuation: 28/66 = 42% Continuation: 32/71 = 45%</td>
<td>Excluded patients on narcotic analgesics</td>
</tr>
<tr>
<td>Arai et al (2015)</td>
<td>Fentanyl patch</td>
<td>Symptomatic treatment of pain</td>
<td>150 opioid-naïve patients with low back pain or pain due to osteoarthritis. Only patients without AEs and with sufficient pain relief on fentanyl during a 20-d run-in period were included</td>
<td>Design D. Blinded with 20 days run-in period and with 1:1 discontinuation</td>
<td>12 wk</td>
<td>Discontinuation: 38/77 = 49% Continuation: 36/73 = 49%</td>
<td>Discontinuation: 29/77 = 38% Continuation: 21/73 = 29%</td>
<td>During run-in, 15% (33/218) discontinued treatment because of AEs and 9% (20/218) were not eligible for discontinuation because of lack of pain relief. The change in pain scores favored continuation; change in VAS of -9.6 mm vs 0.3 mm, adjusted mean difference = 8.7 mm, 95% CI: 2.4 to 15.0 mm.</td>
</tr>
<tr>
<td>Arai et al (2015)</td>
<td>Fentanyl patch</td>
<td>Symptomatic treatment of pain</td>
<td>163 opioid-naïve patients with pain due to post-herpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain. Only patients without AEs and with sufficient pain relief on fentanyl during a 20-d run-in period were included</td>
<td>Design D. Blinded with 20 days run-in period and with 1:1 discontinuation</td>
<td>12 weeks</td>
<td>Discontinuation: 51/79 = 65% Continuation: 37/84 = 44%</td>
<td>Discontinuation: 35/79 = 44% Continuation: 18/84 = 21%</td>
<td>During run-in, 12% (33/280) discontinued treatment due to AEs and 18% (50/280) were not eligible for discontinuation due to lack of pain relief. The change in pain scores favored continuation; change in VAS of -9.6 mm vs 0.3 mm, adjusted mean difference = 8.7 mm, 95% CI: 2.4 to 15.0 mm.</td>
</tr>
<tr>
<td>Holmes et al (2004)</td>
<td>Donepezil</td>
<td>Symptomatic treatment of Alzheimer’s disease</td>
<td>134 treatment-naïve patients with mild to moderate Alzheimer’s disease and marked neuropsychiatric symptoms; Neuropsychiatric Inventory (NPI &gt; 11)</td>
<td>Design A. Blinded with 12 wk run-in period and 3:2 discontinuation</td>
<td>12 wk</td>
<td>Discontinuation: 10/55 = 18% Continuation: 6/41 = 15%</td>
<td>Discontinuation: 6/55 = 11% Continuation: 2/41 = 5%</td>
<td>There were differences in cognition, neuropsychiatric symptoms, and caregiver’s distress in favor of continuation; change in Mini Mental State Examination (MMSE) scores of −0.1 vs −1.8, P = .02; change in NPI of −2.9 vs 3.3, P = .02; and change in NPI distress score of −2.0 vs 1.0, P = .01</td>
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<tr>
<td>Study</td>
<td>Drug</td>
<td>Symptomatic treatment of Alzheimer's disease</td>
<td>Design</td>
<td>Discontinuation:</td>
<td>Continuation:</td>
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<td>20/103 = 19%</td>
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<td>43/72 = 60%</td>
<td>23/73 = 32%</td>
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<td>11/72 = 15%</td>
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<td>44/63 = 70%</td>
<td>40/76 = 53%</td>
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<td>26/63 = 41%</td>
<td>23/76 = 30%</td>
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<td>galantamine,</td>
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<td>4/19 = 21%</td>
<td>3/21 = 14%</td>
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<td></td>
<td>rivastigmine</td>
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<td>7/19 = 37%</td>
<td>6/21 = 29%</td>
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Multiple different cholinesterase inhibitors discontinued (continued on next page)
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Medicine</th>
<th>Discontinued</th>
<th>Indication</th>
<th>Population</th>
<th>Design (See Figure 3)</th>
<th>Follow-Up Duration</th>
<th>Dropouts</th>
<th>Disease Recurrence</th>
<th>Other Relevant Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ory-Magne et al (2014)</td>
<td>Amantadine</td>
<td>Symptomatic treatment of levodopa-induced dyskinesia</td>
<td>56 amantadine-treated patients with Parkinson’s disease and levodopa-induced dyskinesia</td>
<td>Design A. Blinded without a run-in period and 1:1 discontinuation</td>
<td>3 mo</td>
<td>Discontinuation: 24/29 = 83% Continuation: 5/27 = 19%</td>
<td>Discontinuation: 18/29 = 62% Continuation: 3/27 = 11%</td>
<td>The change in dyskinesia (measured with the Unified Parkinson’s Disease Rating Scale dyskinesia subscore) was worse in the discontinuation group (1.7) compared with the continuation group (0.2), P = .003</td>
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<tr>
<td>Biaggioni et al (2015)</td>
<td>Droxidopa</td>
<td>Symptomatic treatment of neurogenic orthostatic hypotension</td>
<td>101 patients with symptomatic neurogenic orthostatic hypotension due to Parkinson’s disease, multiple system atrophy, pure autonomic failure, or non-diabetic autonomic neuropathy. Only patients without AEs and with sufficient effect of the treatment during a 14-d run-in period were included</td>
<td>Design D. Blinded with 14-d run-in period and 1:1 discontinuation</td>
<td>14 d</td>
<td>Discontinuation: 8/51 = 16% Continuation: 6/50 = 12%</td>
<td>Discontinuation: 2/51 = 4% Continuation: 1/50 = 2%</td>
<td>During run-in, 24% (43/181) discontinued treatment because of AEs and 13% (24/181) were not eligible for discontinuation because of lack of effect. There was no statistically significant difference in the change from baseline in symptoms of dizziness and lightheadedness or systolic standing blood pressure between the discontinuation group and the continuation group.</td>
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<tr>
<td>Tse et al (2008)</td>
<td>Levodopa</td>
<td>Symptomatic treatment of Parkinson’s disease</td>
<td>11 levodopa-treated, institutionalized patients with Parkinson’s disease and dementia</td>
<td>Design A without a run-in period and 1:1 discontinuation blinded</td>
<td>4 wk</td>
<td>Discontinuation: 1/6 = 17% Continuation: 0/5 = 0%</td>
<td>Discontinuation: 1/6 = 17% Continuation: 0/5 = 0%</td>
<td>There were no statistically significant changes in cognitive, behavioral, or motor function between the discontinuation and continuation groups.</td>
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</tr>
<tr>
<td>Psychiatry Findlay et al (1989)</td>
<td>Thioridazine</td>
<td>Symptomatic treatment of behavioral and psychological symptoms of dementia (BPSD)</td>
<td>36 thioridazine-treated women with Alzheimer’s disease and BPSD who were admitted to a long-stay psychogeriatric ward</td>
<td>Design A. Blinded without a run-in period and 1:1 discontinuation</td>
<td>4 wk</td>
<td>Discontinuation: 0/18 = 0% Continuation: 0/18 = 0%</td>
<td>Not reported</td>
<td>There were no statistically significant differences between the 2 groups regarding mental function, mobility, balance, or orthostatic blood pressure</td>
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<tr>
<td>Study</td>
<td>Treatment</td>
<td>Symptomatic/Preventive Treatment</td>
<td>Patients</td>
<td>Design</td>
<td>Discontinuation:</td>
<td>Continuation:</td>
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<td>27/40 = 68%</td>
<td>30/70 = 43%</td>
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<td>23/40 = 58%</td>
<td>22/70 = 31%</td>
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<td>28/63 = 44%</td>
<td>19/65 = 29%</td>
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<td>13/63 = 21%</td>
<td>4/65 = 6%</td>
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<td>3/6 = 50%</td>
<td>4/6 = 67%</td>
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<td>3/6 = 33%</td>
<td>4/6 = 33%</td>
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</table>

During run-in, 14% (6/44) discontinued treatment because of AEs and 20% (9/44) were not eligible for discontinuation because of lack of effect. The time to relapse was shorter in the discontinuation group (mean = 5.8 wk) compared with the continuation group (mean = 8.0 wk); log rank test, P = .04.

Depressive symptoms increased more in the discontinuation group than the continuation group; Cornell scale 6.03 vs 4.42, mean difference adjusted for baseline values = 2.89, 95% CI: 1.02-4.76.

The discontinuation group experienced less AEs, especially urinary urgency at night, urination of more than usual volumes, urinary incontinence, and neurotoxicity (ie, hand tremor, lightheadedness, dizziness, and unsteady gait); lower mean composite side-effect symptom score (no estimates reported), P < .05 (continued on next page).
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Medicine</th>
<th>Indication</th>
<th>Population</th>
<th>Design (See Figure 3)</th>
<th>Follow-Up Duration</th>
<th>Discontinuation</th>
<th>Disease Recurrence</th>
<th>Other Relevant Results and Comments</th>
</tr>
</thead>
</table>
| Klysner et al (2002)     | Citalopram                       | Symptomatic and preventive treatment of depression | 121 patients with unipolar major depressive episode of at least moderate severity without antidepressive treatment. Only patients without AEs and with sufficient effect of citalopram during a 24-wk run-in period were included | Design D. Blinded with a 24-wk run-in phase and 1:1 discontinuation | 48 wk              | Discontinuation: 49/61 = 80%  
Continuation: 34/60 = 57% | Discontinuation: 38/61 = 62%  
Continuation: 18/60 = 30% | During run-in, 17% (39/230) discontinued treatment because of AEs and 6% (14/230) were not eligible for discontinuation because of lack of efficacy. The time to recurrence differed significantly between the treatment groups in favor of continuation; HR = 0.32, 95% CI: 0.19-0.56, log-rank test P < .001 |
| Wilson et al (2003)      | Sertraline                       | Symptomatic and preventive treatment of depression | 113 patients with major depressive episode of at least moderate severity without antidepressive treatment. Only patients without AEs and with sufficient effect of sertraline during a 24- to 28-wk run-in period were included | Design D. Blinded with a 24- to 28-wk run-in period and 1:1 discontinuation | 100 wk             | Discontinuation: 43/57 = 75%  
Continuation: 39/56 = 70% | Discontinuation: 30/57 = 53%  
Continuation: 25/56 = 45% | During run-in, 26% (66/254) discontinued treatment because of AEs and 11% (29/254) were not eligible for discontinuation because of lack of efficacy. |
| Ulfvarson et al (2003)   | Citalopram, sertraline           | Symptomatic and preventive treatment of depression | 70 SSRI-treated nursing home residents without a history of depression, anxiety, or dementia | Design A. Blinded without a run-in period and 1:1 discontinuation | 6 mo               | Discontinuation: 10/35 = 29%  
Continuation: 8/35 = 23% | Discontinuation: 7/35 = 20%  
Continuation: 0/35 = 0% | There were no statistically significant differences in depression rating scale, global assessment of functioning, health-related quality of life, symptoms of depression or side effects of SSRIs between the discontinuation and continuation group. |
| Habraken et al (1997)    | Lorazepam                       | Symptomatic treatment of insomnia   | 55 nursing home residents without dementia or other serious medical diseases and with at least 1 y of stable benzodiazepine treatment | Design A. Blinded with a run-in period and 1:1 discontinuation | 1 y                | Discontinuation: 10/27 = 37%  
Continuation: 9/28 = 32% | Discontinuation: 5/27 = 19%  
Continuation: 2/28 = 7% | All benzodiazepines were switched to lorazepam before randomization. The discontinuation group was tapered over 5 wk. There was no statistically significant difference in the level of daily functioning between the discontinuation and continuation group. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Population</th>
<th>Design</th>
<th>Duration</th>
<th>Discontinuation:</th>
<th>Continuation:</th>
<th>Dropout</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curran et al (2003) 37</td>
<td>Temazepam, nitrazepam, loprazolam</td>
<td>Symptomatic treatment of insomnia 104 patients without dementia or other diseases associated with cognitive impairment and with at least 6 mo use of benzodiazepines</td>
<td>Design A (at 12 weeks). Blinded without a run-in period and 1:1 discontinuation</td>
<td>12 wk</td>
<td>7/55 = 13%</td>
<td>6/49 = 12%</td>
<td>Not reported</td>
<td>The discontinuation group was tapered over 4-6 wk. There were no statistically significant differences in sleep quality and several cognitive tests between the discontinuation group and the continuation group.</td>
</tr>
<tr>
<td>O'Brien et al (2001) 38</td>
<td>Beclomethasone dipropionate</td>
<td>Symptomatic and preventive treatment of chronic obstructive pulmonary disease (COPD) 24 outpatients with severe irreversible airway obstruction (mean forced expiratory volume in 1 second [FEV1] 47% of predicted)</td>
<td>Design E. Blinded crossover trial</td>
<td>6 weeks per phase</td>
<td>Crossover trial with randomized order of discontinuation and continuation. Dropout per phase not reported. Dropout during the entire study: 9/24 = 38%</td>
<td>Discontinuation phase: 3/18 = 17% Continuation phase: 0/16 = 0%</td>
<td>Dropout during entire study: 9/24 = 38%</td>
<td>There were no statistically significant differences in lung function or walking distance between the discontinuation phase and the continuation phase. (continued on next page)</td>
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</table>
### Supplementary Table 1 (continued)

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Medicine Discontinued</th>
<th>Indication</th>
<th>Population</th>
<th>Design (See Figure 3)</th>
<th>Follow-Up Duration</th>
<th>Dropouts</th>
<th>Disease Recurrence</th>
<th>Other Relevant Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choudhury et al (2007)</td>
<td>Fluticasone propionate</td>
<td>Symptomatic and preventive treatment of chronic obstructive pulmonary disease (COPD)</td>
<td>260 patients with COPD with irreversible airway obstruction and no other chronic active lung diseases treated with inhaled corticosteroids</td>
<td>Design A. Blinded with a run-in period and 1:1 discontinuation</td>
<td>1 y</td>
<td>Discontinuation: 78/132 = 59%</td>
<td>Discontinuation: 61/132 = 46%</td>
<td>In the per-protocol analysis, there was an increased risk of exacerbations in the discontinuation group compared with the continuation group; 279 exacerbations during a mean study duration of 179 d vs 293 exacerbations during a mean study duration of 235 d, RR = 1.48, 95% CI: 1.17-1.86. Time to first exacerbation was shorter in the discontinuation group (median 44 d) compared with the continuation group (median 63 d); log-rank test, <em>P</em> = .05, adjusted Cox regression analysis OR = 1.43, 95% CI: 1.08-1.96. The discontinuation group had an increase in wheeze (OR = 1.83, 95% CI: 1.06-3.18), an increase in shortness of breath (OR = 2.11, 95% CI: 1.25-3.57), and cough (during the first 3 mo; OR = 1.95, 95% CI: 1.16-3.29). There were no statistically significant differences in sputum production, lung function, or quality of life between the 2 groups.</td>
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</tbody>
</table>
Borrill et al (2009) Fluticasone propionate and salmeterol, fixed dose combination

Symptomatic and preventive treatment of chronic obstructive pulmonary disease (COPD)

14 patients with stable, moderate COPD (GOLD stage-II)

Design A. Nonblinded without a run-in period and 3:2 discontinuation

6 wk Discontinuation: 4/9 = 44% Continuation: 0/5 = 0%

Discontinuation: 4/9 = 44% Continuation: 0/5 = 0%

There was a decrease in lung function in the discontinuation group compared with the continuation group; difference in change in FEV1 = 0.35, P = .017. The percentage of sputum neutrophil increased more in the continuation group compared with the continuation group; difference in change from baseline = 16.5%, P = .03.


Symptomatic and preventive treatment of chronic obstructive pulmonary disease (COPD)

38 patients with steroid-dependent COPD

Design C. Blinded with a run-in period with addition of ICS and with 1:1 discontinuation

6 mo Discontinuation: 10/18 = 56% Continuation: 8/20 = 40%

Discontinuation: 14/18 = 78% Continuation: 14/20 = 70%

There were no statistically significant differences regarding exacerbations, lung function, or quality of life between the 2 groups. There was a difference in change in weight from baseline between the discontinuation group (−4.8 kg) and the continuation group (0.5 kg); P = .007.

Fabricius et al (1990) Terazosin

Symptomatic treatment of lower urinary tract symptoms (LUTS)

30 men with moderate obstructive symptoms due to benign prostatic hyperplasia (BPH). Only patients with sufficient effect of terazosin during a 24-wk run-in period were included.

Design D. Blinded with a 24-week run-in period and 1:1 discontinuation

12 wk Discontinuation: 0/15 = 0% Continuation: 0/15 = 0%

Not reported

During run-in, 47% (27/57) were not eligible for discontinuation because of lack of efficacy and 30% (17/57) experienced adverse events.


Symptomatic treatment of LUTS

305 men with moderate to severe urinary symptoms due to BPH

Design C. Blinded with a run-in period with dutasteride and tamsulosin and with 1:1 discontinuation

6 wk Discontinuation: 2/151 = 1% Continuation: 1/154 = 1%

Discontinuation: 35/151 = 23% Continuation: 14/154 = 9%

There was a difference in urinary symptoms with more patients feeling the same or better in the continuation group (91%) compared with the discontinuation group (77%); difference = 14%, 95% CI: 4%-18%; P = .001.

(continued on next page)
### Supplementary Table 1 (continued)

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Medicine</th>
<th>Indication</th>
<th>Population</th>
<th>Design (See Figure 3)</th>
<th>Follow-Up Duration</th>
<th>Dropouts</th>
<th>Disease Recurrence</th>
<th>Other Relevant Results and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Tamsulosin | Symptomatic treatment of LUTS | 86 treatment-naïve men with moderate urinary symptoms due to BPH | Design C. Nonblinded with a run-in period with dutasteride and tamsulosin and with 1:1 discontinuation | 24 wk | Discontinuation: 10/43 = 23%  
Continuation: 7/43 = 16% | Discontinuation: 6/43 = 14%  
Continuation: 4/43 = 9% | There was no statistically significant differences between groups in voiding symptoms and related measures, quality of life, adverse effects, or blood pressure. |
| Matsukawa et al (2017) |
| Silodosin | Symptomatic treatment of LUTS | 132 treatment-naïve men with moderate to severe urinary symptoms due to BPH | Design C. Nonblinded with a run-in period with dutasteride and silodosin and with 1:1 discontinuation | 12 mo | Discontinuation: 6/66 = 9%  
Continuation: 9/66 = 14% | Discontinuation: 23/66 = 35%  
Continuation: 15/66 = 23% | There was no statistically significant differences between groups in subjective symptoms or bladder outlet obstruction. |
### Supplementary Table 2
Risk of Bias Assessment of the Included Studies.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Medicine(s) Discontinued</th>
<th>Risk of Bias Assessment</th>
<th>Randomization Process</th>
<th>Differential Dropout Rate: Blinding, Tapering, etc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheppard et al (2021)</td>
<td>Antihypertensives</td>
<td>Some concern</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Nijst et al (2020)</td>
<td>Beta-blockers</td>
<td>Low risk</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Wright et al (2017)</td>
<td>Alendronate</td>
<td>Low risk</td>
<td>Some concern</td>
<td></td>
</tr>
<tr>
<td>Black et al (2012)</td>
<td>Zoledronic acid</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Arai et al (2015), study 1</td>
<td>Fentanyl patch</td>
<td>Some concern</td>
<td>Some concern</td>
<td></td>
</tr>
<tr>
<td>Arai et al (2015), study 2</td>
<td>Fentanyl patch</td>
<td>Some concern</td>
<td>Some concern</td>
<td></td>
</tr>
<tr>
<td>Gaudig et al (2011)</td>
<td>Galantamine</td>
<td>Some concern</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Scarpini et al (2011)</td>
<td>Galantamine</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Herrmann et al (2016)</td>
<td>Cholinesterase inhibitors</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Findlay et al (1989)</td>
<td>Thoridazine</td>
<td>Some concern</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Devanand et al (2011)</td>
<td>Haloperidol</td>
<td>Some concern</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Bergh et al (2012)</td>
<td>SSRIs</td>
<td>Low risk</td>
<td>Some concern</td>
<td></td>
</tr>
<tr>
<td>Hardy et al (1997)</td>
<td>Lithium</td>
<td>Some concern</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Choudhury et al (2007)</td>
<td>Inhaled fluticasone</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Borrelli et al (2009)</td>
<td>Inhaled fluticasone + salmeterol</td>
<td>Some concern</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Fabricius et al (1990)</td>
<td>Terazosin</td>
<td>Some concern</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Lee et al (2012)</td>
<td>Tamsulosin</td>
<td>High risk</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>Matsukawa et al (2017)</td>
<td>Silodosin</td>
<td>Low risk</td>
<td>High risk</td>
<td></td>
</tr>
</tbody>
</table>
### Supplementary Table 3
Harms Reported in the Included Studies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Medicine(s) Discontinued</th>
<th>Discontinuation Group</th>
<th>Continuation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>George et al (2003)</td>
<td>Nitrates</td>
<td>8 with recurrent angina with prompt effect of reinstated therapy (1 of the patients hospitalized, catheterized, and underwent coronary angioplasty)</td>
<td>1 patient with angina</td>
</tr>
<tr>
<td>van Kraaij et al (1999 and 2000)</td>
<td>Furosemide</td>
<td>2 recurrence of congestive heart failure, 2 requested restart because ankle edema without heart failure, 1 hypertension</td>
<td>1 recurrence of congestive heart failure</td>
</tr>
<tr>
<td>Kutner et al (2015)</td>
<td>Statins</td>
<td>Not specified per group. There were 33 AEs experienced by 19 of the patients (5.0%). No serious AEs were determined to be study related</td>
<td></td>
</tr>
<tr>
<td>Sheppard et al (2021)</td>
<td>Antihypertensives</td>
<td>AEs not reported per group in this post hoc analysis</td>
<td></td>
</tr>
<tr>
<td>Nijst et al (2020)</td>
<td>Beta-blockers</td>
<td>1 death noncardiovascular cause, 1 disease recurrence, 6 supraventricular tachycardia, 1 nonsustained ventricular tachycardia</td>
<td>2 disease recurrence, 1 death noncardiovascular cause</td>
</tr>
<tr>
<td>Greenspan et al (2002)</td>
<td>Alendronate</td>
<td>AEs not described for the individual groups. Overall, no difference in AEs between the discontinuation and continuation group, including no difference in gastrointestinal AEs</td>
<td>2 upper gastrointestinal symptoms, 2 bone pain, 1 allergic skin reactions, 1 gastric pain</td>
</tr>
<tr>
<td>Michalská et al (2006)</td>
<td>Alendronate</td>
<td>1 leg cramp, 1 upper gastrointestinal symptoms</td>
<td></td>
</tr>
<tr>
<td>Wright et al (2017)</td>
<td>Alendronate</td>
<td>No AEs were reported</td>
<td></td>
</tr>
<tr>
<td>Black et al (2012)</td>
<td>Zoledronic acid</td>
<td>Total patients with any AE = 552; total patients with any SAE = 168; total patients discontinuing because of AE = 11; renal events = 26; any of the most common postdose symptoms (pyrexia, myalgia, influenza-like illness, headache, and arthralgia): First year = 29, second year = 14, third year = 7; cardiovascular AEs: 52 arrhythmia, 13 atrial fibrillation, 9 stroke, 4 myocardial infarction, 93 hypertension, 3 death from cardiovascular causes</td>
<td></td>
</tr>
<tr>
<td>Cibere et al (2004)</td>
<td>Glucosamine</td>
<td>No SAEs were reported during the study, and there were no differences in AEs between the glucosamine and placebo groups</td>
<td></td>
</tr>
<tr>
<td>Arai et al (2015), study 1</td>
<td>Fentanyl patch</td>
<td>No AEs were reported</td>
<td></td>
</tr>
<tr>
<td>Arai et al (2015), study 2</td>
<td>Fentanyl patch</td>
<td>12 nervous system, 9 infections and infestations, 5 metabolism and nutrition disorders, 5 psychiatric disorders, 15 gastrointestinal disorders, 13 general disorders and administration, 1 opioid withdrawal syndrome</td>
<td></td>
</tr>
<tr>
<td>Holmes et al (2004)</td>
<td>Donepezil</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Johannsen et al (2006)</td>
<td>Donepezil</td>
<td>Any AE (n = 33): 10 treatment-related AEs, 6 digestive system, 8 nervous system, 10 body as a whole, 4 musculoskeletal system, 7 respiratory system, 4 cardiovascular system, 2 urogenital system</td>
<td></td>
</tr>
<tr>
<td>Howard et al (2012)</td>
<td>Donepezil</td>
<td>Only SAEs reported. Discontinuation group: total of 46 SAEs; 12 fall, 6 respiratory tract infection, 2 urogenital tract infection, 7 deterioration of AD, 4 behavioral symptoms of AD, 2 gastrointestinal, 3 stroke, 1 cardiac, 1 dysphagia, 2 psychosis, 2 unknown (died), 1 venous embolus, 3 other</td>
<td></td>
</tr>
<tr>
<td>Gaudig et al (2011)</td>
<td>Galantamine</td>
<td>Total patients with any AE = 16; total patients with any SAE = 1; total patients discontinuing because of AE = 0; AEs occurring in at least 2.5% of patients: 3 headache, 1 confusion, 0 dizziness, 0 agitation, 1 tremor, 0 vomiting</td>
<td></td>
</tr>
</tbody>
</table>

 AE: Any event; SAE: Serious adverse event; AD: Alzheimer’s disease; DVT: Deep vein thrombosis; OAC: Oral anticoagulant; CPR: Cardiopulmonary resuscitation; ECG: Electrocardiogram; PAC: Pericardial effusion; ICD: Implantable cardioverter defibrillator; MRI: Magnetic resonance imaging; NIHSS: National Institutes of Health Stroke Scale; J. Kornholt et al. / JAMDA 23 (2022) 1926.e11
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Drug(s)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarpini et al (2011)</td>
<td>Galantamine</td>
<td>Assumed related: 1 cardiac disorder, 1 investigation, 3 psychiatric disorder; assumed not related: 1 gastrointestinal disorder, 2 general disorders and administration site conditions, 2 infections and infestations, 3 investigations, 1 metabolism and nutrition disorder, 1 musculoskeletal and connective tissue disorder, 1 neoplasm benign, malignant, and unspecified, 7 nervous system disorder, 5 psychiatric disorder, 1 renal and urinary disorder</td>
</tr>
<tr>
<td>Herrmann et al (2016)</td>
<td>Cholinesterase inhibitors</td>
<td>5 unintentional weight loss, 3 falls, 1 oval thrush, 1 IV due to poor appetite, 1 respiratory tract infection, 1 cognitive decline, 3 deterioration in behavior, 1 bowel obstruction</td>
</tr>
<tr>
<td>Ory-Magne et al (2014)</td>
<td>Amantadine</td>
<td>19 worsening of dyskinesia, 8 worsening of parkinsonism, 4 pain, 2 fatigue, 1 sweat/flushing, 2 asthenia, 2 nausea/vomiting, 2 drowsiness, 1 cephalgia, 2 cough</td>
</tr>
<tr>
<td>Biaggioni et al (2015)</td>
<td>Droxidopa</td>
<td>Total 19 (37%) patients experienced ≥ 1 AEs; these included 4 headache, 1 dizziness, 1 fatigue, 6 falls, 2 nausea, 1 diarrhea, 2 urinary tract infection</td>
</tr>
<tr>
<td>Tse et al (2008)</td>
<td>Levodopa</td>
<td>1 fever and worsening of mental status and parkinsonian symptoms</td>
</tr>
<tr>
<td>Findlay et al (1989)</td>
<td>Thioridazine</td>
<td>None described</td>
</tr>
<tr>
<td>Devanand et al (2011)</td>
<td>Haloperidol</td>
<td>AEs not systematically described</td>
</tr>
<tr>
<td>Devanand et al (2012)</td>
<td>Risperidone</td>
<td>SAEs: 1 died, 1 cardiovascular events, 1 neurologic event, 2 agitation-aggression, 1 pulmonary event, 2 other SAE. AE: 10 extrapyramidal signs, 10 akathisia or restlessness, 7 sedation, 2 insomnia, 8 confusion, 3 agitation-aggression, 1 falls, 3 nausea or vomiting</td>
</tr>
<tr>
<td>Bergh et al (2012)</td>
<td>SSRIs</td>
<td>AEs not systematically described; 13 increased depressive or neuropsychiatric symptoms</td>
</tr>
<tr>
<td>Hardy et al (1997)</td>
<td>Lithium</td>
<td>AEs not systematically described; AEs were registered using a composite side-effect symptom score; at all clinic visits, the mean score was less in the discontinuation group compared with the continuation group (P &lt; .05)</td>
</tr>
<tr>
<td>Klysner et al (2002)</td>
<td>Citalopram</td>
<td>2 nausea, 3 diarrhea, 4 headache, 3 increased sweating, 4 dizziness, 6 fatigue, 3 hot flushes, 1 vertigo, 2 dry mouth, 3 insomnia, 1 vomiting, 1 abdominal pain, 2 hypokalemia, 2 hypertension, 4 influenza-like symptoms, 4 traumatic injury, 1 pain, 2 back pain, 1 cystitis, 2 bronchitis</td>
</tr>
<tr>
<td>Ulfvarson et al (2003)</td>
<td>Citalopram, sertraline</td>
<td>AEs not systematically described</td>
</tr>
<tr>
<td>Habraken et al (1997)</td>
<td>Lorazepam</td>
<td>AEs not systematically described</td>
</tr>
<tr>
<td>Curran et al (2003)</td>
<td>Benzodiazepines</td>
<td>No AEs were reported</td>
</tr>
<tr>
<td>O'Brien et al (2001)</td>
<td>Inhaled beclometasone</td>
<td>3 severe exacerbations during discontinuation</td>
</tr>
<tr>
<td>Choudhury et al (2007)</td>
<td>Inhaled fluticasone</td>
<td>There was no significant difference in reporting of skin bruising, thinning of skin, sore throat, oral thrush, or hoarseness of voice between fluticasone and placebo groups during the study; there were 3 COPD-related deaths in the continuation group</td>
</tr>
<tr>
<td>Borrill et al (2009)</td>
<td>Inhaled fluticasone + salmeterol</td>
<td>2 unspecified AEs</td>
</tr>
<tr>
<td>Rice et al (2000)</td>
<td>Prednisone</td>
<td>No AEs were reported</td>
</tr>
<tr>
<td>Fabricius et al (1990)</td>
<td>Terazosin</td>
<td>No AEs during the discontinuation phase</td>
</tr>
<tr>
<td>Barkin et al (2003)</td>
<td>Tamsulosin</td>
<td>2 dysuria, 2 urinary frequency, 2 urinary infections, 2 ejaculation disorders, 2 musculoskeletal pain, 2 viral respiratory tract infection</td>
</tr>
<tr>
<td>Lee et al (2012)</td>
<td>Tamsulosin</td>
<td>AEs not specified per group; in total: 2 reduced libido, 2 ejaculatory problem</td>
</tr>
<tr>
<td>Matsukawa et al (2017)</td>
<td>Silodosin</td>
<td>1 chest pain and 1 anhema</td>
</tr>
</tbody>
</table>

AE, adverse events; COPD, chronic obstructive pulmonary disorder; SAEs, serious adverse events.
References


