to moderate COPD (FEV1 <80% of predicted).\(^1\) Eleven studies (n=185) assessed use of beta-blockers for 2 days to 16 weeks (mean duration 5.3 weeks) compared with placebo and found no significant difference in percent change from baseline for FEV1 (mean difference [MD] –2.7%; 95% CI, –6.0 to 0.57) or respiratory symptoms such as self-reported wheezing, dyspnea, breathlessness, acute shortness of breath, or COPD exacerbations (risk difference [RD] –0.01; 95% CI, –0.06 to 0.04). Three studies (n=87) showed no significant difference in percent change from baseline for FEV1 response to inhaled beta-2 agonist treatment in patients taking beta-blockers compared with placebo (MD –0.70%; 95% CI, –5.0 to 3.6). Eleven studies (n=131) evaluated single-dose beta-blocker use and similarly showed no significant changes in these endpoints.

A systematic review of 9 retrospective cohort trials (N=99,877) assessed beta-blocker effect on mortality in patients with COPD.\(^2\) Studies with clearly defined COPD characteristics, defined beta-blocker use, and results presented in relative risks and odds ratios with confidence intervals were included. Cardioselectivity of the beta-blockers was not specified in 6 of the trials; 2 trials assessed cardioselective formulations; 1 trial assessed both cardioselective and noncardioselective drugs. Five studies (n=88,879) included patients with COPD who also had heart failure (HF) or vascular disease.

The relative risk of COPD mortality in patients using beta-blockers was 0.69 (95% CI, 0.62–0.78) compared with patients not using beta-blockers. However, a funnel plot demonstrates publication bias with no small negative studies published.\(^2\)

A subsequent retrospective cohort study evaluated the effects of beta-blocker use on 60-day mortality and combined endpoint of 60- to 90-day mortality or rehospitalization in patients with systolic HF and COPD.\(^3\) Of the 2,670 patients, 725 had COPD and HF with 70% of those prescribed beta-blockers (40% cardioselective, 60% noncardioselective). Mortality was decreased at 60 days in patients with COPD taking noncardioselective beta-blockers compared with no beta-blocker (HR 0.47; 95% CI, 0.25–0.89), but no difference was noted in patients taking cardioselective beta-blockers compared with no beta-blocker. Mortality at 60 to 90 days or rehospitalization did not differ between beta-blocker use or nonuse.

Conversely, a prospective cohort study of 2,249 patients with oxygen-dependent COPD found that beta-blockers were associated with an increase in mortality over a mean follow-up of 1.1 years, compared with other cardiovascular drug use (HR 1.2; 95% CI, 1.0–1.4).\(^4\)

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**Does phentermine use for weight loss have significant adverse effects?**

**Evidence-Based Answer**

Anorexiant drugs are associated with primary pulmonary hypertension (PPH); however, no reports specifically link phentermine to this condition (SOR: B, case control study and case series). Case reports have linked phentermine with stroke and peripheral arterial vasospasm (SOR: C, case reports).

A case-control study of 35 patients 18 to 20 years old diagnosed with PPH and 85 matched controls without PPH looked for an association between PPH and appetite suppressant use.\(^1\) Twenty-three of the patients with PPH had taken appetite suppressants, mostly fenfluramine, but 2 patients took compounds containing phentermine and fenfluramine. No patients had taken only phentermine. Of the 85 controls matched for age, sex, geographic area, and healthcare utilization, 5 reported anorexiant use, but none used phentermine. The differences in appetite suppressant use between groups was significant (66% vs 6%; \(P<.0001\)). A subgroup analysis of phentermine use was not reported.

A prospective surveillance study followed 205 patients diagnosed with PPH at 12 large referral centers for about a year.\(^2\) Fourteen patients had a history of phentermine use (6.8%), but this history was not significantly associated with PPH (OR 0.6; 95% CI, 0.2–2.2). The study did find an association between fenfluramine use >6 months (14 patients) and PPH (OR 7.5; 95% CI, 1.7–32).

A case report described 2 young patients taking phentermine who had strokes.\(^3\) The first patient was a 41-year-old woman with hypercholesterolemia, who sustained a right occipital infarct after taking...
phentermine for 8 months. The second patient was a 37-year-old woman with 7 days of a parieto-occipital headache, facial numbness, and arm numbness after recently starting phentermine. These symptoms were suspected to be due to a small, deep brainstem infarct.

Another case report detailed a 39-year-old woman without a significant medical history who had an acute episode of left arm and hand coldness, pain, weak pulse, and decreased capillary refill. It was determined that this episode was a result of vasospasm, which resolved after nifedipine administration. The patient had been taking phentermine 15 mg daily, phendimetrazine 35 mg daily, and an unknown amount of unlabeled thyroid medication for weight loss 3 days prior to the episode.

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Are fish oil supplements as effective as gemfibrozil for decreasing elevated triglycerides?

Evidence-Based Answer

The answer is unclear. In patients with hypertriglyceridemia, omega-3 fatty acid and fibric acid derivatives reduce triglyceride levels compared with baseline, but evidence is conflicting whether omega-3 fatty acid supplementation is as effective as gemfibrozil (SOR: C, inconsistent RCTs with disease-oriented outcomes).

In 2012, a single-blind RCT investigated the effect on lipoprotein and glucose metabolism among omega-3 fatty acid (Omacor®), fenofibrate, and placebo in 150 individuals with primary hypertriglyceridemia (serum triglyceride level ≥150 mg/dL). Patients were randomized to receive omega-3 fatty acid 2 g by mouth once daily, fenofibrate 160 mg by mouth once daily, or placebo once daily for 2 months.

Compared with baseline, triglyceride levels significantly decreased from baseline in all 3 groups: the omega-3 fatty acid group (21%; P < .001), the fenofibrate group (29%; P < .001), and the placebo group (9%; P < .01). No significant difference was noted in triglyceride reduction between the omega-3 fatty acid and fenofibrate groups. When compared with placebo, only fenofibrate was associated with a significant reduction in triglyceride levels (P < .05).

In 2011, an RCT with 107 patients (age range 35–70 years) with primary isolated hypertriglyceridemia (serum triglyceride level 200–500 mg/dL) evaluated the lymphocyte-suppressing and systemic anti-inflammatory effects of omega-3 fatty acids and bezafibrate (used in Europe). Lipoprotein levels were obtained for secondary analysis. Patients received oral bezafibrate 200 mg twice daily, omega-3 fatty acid 1 g twice daily, or placebo twice daily for 12 weeks. All groups had a 4-week nonpharmacologic treatment run-in period and then 12 weeks of pharmaotherapy.

Compared with baseline levels, triglycerides were decreased significantly in the omega-3 fatty acid group (31%; P < .01), and in the bezafibrate group (38%; P < .001), but not in the placebo group (6%; P > .05). No difference was noted in triglyceride lowering between the omega-3 fatty acid and bezafibrate groups.

A 2001 randomized, double-blind trial of 89 patients (92% male) with severe hypertriglyceridemia (serum triglyceride level >398 mg/dL) examined the change in serum lipoprotein levels in patients randomized to omega-3 fatty acid (Omacor) 4 g by mouth once daily and gemfibrozil 1,200 mg by mouth once daily. Both groups received oral and written dietary advice during a 6-week run-in period and throughout the study. The primary study objective was to measure change in serum triglycerides between groups.

Compared with baseline, after 12 weeks of therapy, serum triglyceride levels decreased by 29% and 51% in the omega-3 fatty acid and gemfibrozil groups, respectively (P < .0001 for both groups). When compared with omega-3 fatty acid, gemfibrozil was associated with a greater reduction in triglyceride levels (P = .007).

A double-blind, double-dummy RCT in 2000 compared the effects of omega-3 fatty acid and gemfibrozil on lipid and lipoprotein levels, low-density lipoprotein (LDL) heterogeneity, and LDL oxidizability in 28 patients with primary hypertriglyceridemia (serum triglyceride level 354–2,478 mg/dL). Patients were randomized to gemfibrozil 1,200 mg by mouth daily or omega-3 fatty acid (Omacor) 4 g by mouth daily. Both groups underwent a 6-week washout and run-in period prior to randomization.