EVIDENCE PROFILES ONLINE SUPPLEMENT

Evaluation and Management of Obesity Hypoventilation Syndrome

An Official American Thoracic Society Clinical Practice Guideline

Babak Mokhlesi, Juan Fernando Masa, Jan L. Brozek, Indira Gurubhagavatula, Patrick B. Murphy, Amanda J. Piper, Aiman Tulaimat, Majid Afshar, Jay S. Balachandran, Raed A. Dweik, Ronald R. Grunstein, Nicholas Hart, Roop Kaw, Geraldo Lorenzi-Filho, Sushmita Pamidi, Bhakti K. Patel, Susheel P. Patil, Jean Louis Pépin, Israa Soghier, Maximiliano Tamae Kakazu, Mihaela Teodorescu; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

Evidence table E1: Should serum bicarbonate (HCO_3^-) rather than partial pressure of carbon dioxide in arterial blood ($PaCO_2$) be used to screen for OHS in obese adults with sleep-disordered breathing?

Patient or population: obese adults with OSA

New test: serum bicarbonate | **Cut-off value**: 27 mmol/l

Pooled sensitivity: 0.86 (95% CI: 0.70 to 0.94) | **Pooled specificity**: 0.77 (95% CI: 0.60 to 0.89)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% Typically seen in patients with OSA and BMI 30-34	**Prevalence 10%** Typically seen in patients with OSA and BMI 35-40	**Prevalence 20%** Typically seen in patients with OSA and BMI over 40		
True positives	**43** (35 to 47)	**86** (70 to 94)	**172** (140 to 188)	1372 (5) [a]	⊕◯◯◯ **VERY LOW**
False negatives	**7** (3 to 15)	**14** (6 to 30)	**28** (12 to 60)		
True negatives	**731** (570 to 845)	**693** (540 to 801)	**616** (480 to 712)	1372 (5) [a]	⊕◯◯◯ **VERY LOW**
False positives	**219** (105 to 380)	**207** (99 to 360)	**184** (88 to 320)		
Inconclusive	Not reported			(0)	-
Complications	Not reported			(0)	-

CI: Confidence interval

Explanations

a. One more study included very few patients with OHS and was excluded from analysis (Borel 2017). Sensitivity analysis including this study did not show a difference in accuracy.

References:

1) Bingol Z, Pihtili A, Cagatay P, Okumus G, Kiyan E. Clinical predictors of obesity hypoventilation syndrome in obese subjects with obstructive sleep apnea. *Respir Care* 2015;60:666-672. *We acknowledge Drs. Esen Kiyan and Züleyha Bingöl for sharing revised data for Table 3 of their original manuscript.
2) Macavei VM, Spurling KJ, Loft J, Makker HK. Diagnostic predictors of obesity-hypoventilation syndrome in patients suspected of having sleep disordered breathing. *J Clin Sleep Med* 2013;9:879-884.
3) Basoglu OK, Tasbakan MS. Comparison of clinical characteristics in patients with obesity hypoventilation syndrome and obese obstructive sleep apnea syndrome: A case-control study. *Clin Respir J* 2013;8:167-174.
4) Borel JC, Guerber F, Jullian-Desayes I, Joyeux-Faure M, Arnol N, Taleux N, et al. Prevalence of obesity hypoventilation syndrome in ambulatory obese patients attending pathology laboratories. *Respirology* 2017;22:1190-1198.
5) Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: Prevalence and predictors in patients with obstructive sleep apnea. *Sleep Breath* 2007;11:117-124.
6) Elsayed AY, El-Shafey MM, Abdelgawad TT, Abdelhady Ali R. Predictors of early diagnosis of obesity hypoventilation syndrome among patients with sleep disordered breathing. *Egypt J Chest Dis Tuberc* 2017;66:453-458.

Evidence table E2: Should adults with OHS be treated with positive airway pressure (PAP)—either continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV)—or not be treated with PAP?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	positive airway pressure (PAP)	no PAP	Relative (95% CI)	Absolute (95% CI)		
Death (RCT) (follow up: range 1 to 2 months)												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/209 (0.0%)	0/205 (0.0%)	not estimable	0 fewer per 1,000 (from 13 fewer to 13 more)	⊕◯◯◯ VERY LOW	CRITICAL
Death (observational studies) (follow up: range 1 months to 7 years)												
21 [1-21]	observational studies	serious [c]	serious [d]	serious [c]	not serious	none	In 1 comparative observational study with 1 year observation mortality was lower in those receiving BiPAP compared to those initially not receiving PAP: 26% vs. 54%; RR: 0.35 (95% CI: 0.23 to 0.55; RD: 35 fewer per 100 (95% CI: 20 to 50 fewer). (Sanchez Gomez 2012). Single-arm studies (case series): In-hospital mortality: PAP: 5.8% (95% CI: 2.3 to 9.3) (Carrillo 2012) no PAP: 15% (95% CI: 12.1 to 17.9) (Marik 2016) Mortality after 1 year: PAP: 4% (range: 4% to 15%) (Blankenburg 2017, Heinemann 2007, Jothieswaran 2015, Piesiak 2013, Salturk 2015, Tabernero Huguet 2016) no PAP: 23.4% (95% CI: 11 to 36) (Nowbar 2004) Mortality at 2 years: PAP: 8% (range: 4 to 27) (Blankenburg 2017, Bouloukaki 2018, Heinemann 2007, Jothieswaran 2015, Tsolaki 2011) no PAP: no data Mortality at 3-5 years: PAP: 19.4% (range: 6 to 36) (Blankenburg 2017, Borel 2013, Budweiser 2007, Jothieswaran 2015, Masa 2015, Palm 2016, Perez de Llano 2005, Priou 2010) no PAP: 19.2% (95% CI: 15.8 to 22.6) among those who survived exacerbation and were discharged from hospital (Marik 2016) Mortality at 7 years: PAP: 26.3% (95% CI: 22.0 to 30.5) (Castro-Anon 2015, Jothieswaran 2015, Ojeda Castillejo 2015) no PAP: no data				⊕◯◯◯ VERY LOW	CRITICAL
Quality of life (assessed with: Functional Outcomes of Sleep Questionnaire (FOSQ) (range of possible scores: 0-120, higher score is better; MID ~?))												
2 [1,3]	randomised trials	serious [a]	not serious	not serious	serious [e]	none	172	112	-	MD 6.59 points more (2.47 more to 10.7 more)	⊕⊕◯◯ LOW	CRITICAL
Resolution of hypercapnia (follow up: range 1 to 2 months; assessed with: $PaCO_2$ <45 mmHg at the end of the study)												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	serious [f]	none	64/177 (36.2%)	32/123 (26.0%)	RR 1.39 (0.97 to 2.00)	10 more per 100 (from 1 fewer to 26 more)	⊕⊕◯◯ LOW	CRITICAL
Resolution of hypercapnia (follow up: range 3 months to 7 years)												
8 [6,8,9,11,19,22,23,24]	observational studies	serious [c]	serious [g]	not serious	not serious	none	Eight series of cases of patients receiving various modes of PAP reported resolution of OHS in 2% to 74% of patients.				⊕◯◯◯ VERY LOW	CRITICAL
Awake hypoxemia (follow up: range 1 to 2 months; assessed with: change from baseline in PaO_2 of 62 mm Hg)												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	serious [e]	none	190	129	-	MD 3.2 mm Hg higher (0.8 higher to 5.5 higher)	⊕⊕◯◯ LOW	IMPORTANT
Awake hypercapnia (follow up: range 1 to 2 months; assessed with: change from baseline in $PaCO_2$ of 51 mm Hg)												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	serious [e]	none	190	129	-	MD 2.4 mm Hg lower (1 lower to 3.8 lower)	⊕⊕◯◯ LOW	IMPORTANT
Nocturnal oxygen saturation <90% [% total sleep time]												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	not serious	none	190	129	-	MD 31.3 % lower (24.5 lower to 38 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Apnea–hypopnea index (AHI) (assessed with: change from baseline of 70 episodes/h)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	151	84	-	MD 50 episodes/h fewer (42 fewer to 58 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Motor vehicle accidents - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Daytime sleepiness (assessed with: change from baseline in Epworth Sleepiness Scale (range of scores: 0-24; lower score is better; MID ~2-3 points))[25]												

3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	serious [e]	none	190	129	-	MD 2.49 points lower (1.03 lower to 3.95 lower)	⊕⊕◯◯ LOW	CRITICAL
Resolution of daytime sleepiness (follow up: 2 months; assessed with: Epworth Sleepiness Scale **≤10 at the end of the study**)												
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	serious [f]	none	111/171 (64.9%)	61/113 (54.0%)	RR 1.21 (0.99 to 1.47) [h]	10 more per 100 (from 2 fewer to 24 more)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular events												
1 [26]	observational studies	serious [i]	not serious	not serious	serious [j]	none	33/204 (16.2%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Exercise and/or functional capacity (follow up: 2 months; assessed with: change from baseline in 6-Minute Walk Distance in meters [MID ~20 to 40 m])												
2 [1,3]	randomised trials	serious [a]	not serious [k]	not serious	serious [l]	none	172	112	-	MD 12 m more (12 fewer to 41 more)	⊕⊕◯◯ LOW	IMPORTANT
Need for daytime supplemental oxygen												
2 [1,3]	randomised trials	serious [a]	serious [m]	not serious	serious [n]	none	43/190 (22.6%)	36/129 (27.9%)	RR 0.79 (0.54 to 1.16)	6 fewer per 100 (from 4 more to 13 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in need for supplemental oxygen (follow up: 2 months; assessed with: PaO_2 >55 mm Hg at the end of the study)												
2 [1,3]	randomised trials	serious [a]	not serious	not serious	serious [f]	none	144/160 (90.0%)	83/106 (78.3%)	RR 1.16 (1.04 to 1.30)	13 more per 100 (from 3 more to 23 more)	⊕⊕◯◯ LOW	IMPORTANT
Quality of sleep (assessed with: change from baseline of 58 arousals/h)												
2 [1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	151	84	-	MD 35.33 arousals fewer (42.81 fewer to 27.85 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of sleep in patients with no severe OSA (follow up: 2 months; assessed with: change from baseline of 22 arousals/h)												
1 [3]	randomised trials	serious [a]	not serious	not serious	serious [o]	none	39	45	-	MD 10 arousals/h fewer (6 fewer to 47 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Hospitalization (follow up: 2 months)												
1 [3]	randomised trials	serious [a]	not serious	not serious	serious [p]	none	There were no hospital admissions in the group receiving PAP and 5 hospital admissions per 100 patients over 2 months (95% CI: 0 to 12) in those not receiving PAP. Hospitalized patients stayed in the hospital for an average of 0.65 days per patient over 2 months (95% CI: 0 to 1.64 days).				⊕⊕◯◯ LOW	CRITICAL
Hospitalization												
5 [4,9,21,24,26]	observational studies	serious [c]	not serious	not serious	serious [q]	none	One comparative observational study found the rate of hospital readmissions in those discharged with BiPAP compared with those initially discharged with no PAP to be 55% vs. 48% (RR: 1.14 (95% CI: 0.83 to 1.56) (Sanchez Gomez 2012). Four series of cases reported the risk of hospitalization in patient receiving PAP: 10% (2.4 to 17.6); 3 months of observation (Howard 2017) 12% (1.0 to 22.6); 1 year of observation (Salturk 2015) 35% (22.4 to 47.9) 4 years of observation (Perez de Llano 2005) 49% (41.7 to 55.4); 5 years of observation (Sánchez Quiroga 2018)				⊕◯◯◯ VERY LOW	IMPORTANT
Length of hospital stay												
4 [4,10,12,16]	observational studies	serious [c]	not serious	serious [c]	not serious	none	Two series of cases of patients who received PAP reported a mean of 16 days (14.5 to 17.5) (Carrillo 2012) and 11 days (10 to 12) (Salturk 2015). Two series of cases that did not receive PAP reported similar length of hospital stay: mean 10 days (9 to 11) (Marik 2016) and 8 days (5 to 11) (Nowbar 2004).				⊕◯◯◯ VERY LOW	IMPORTANT
Emergency department visit (follow up: 2 months)												
1 [3]	randomised trials	serious [a]	not serious	not serious	serious [f]	none	25	35	-	MD 18 visits/100 persons/2 months fewer (32 fewer to 1 more)	⊕⊕◯◯ LOW	IMPORTANT
Emergency Department visit (follow up: 1 year)												
2 [4,26]	observational studies	serious [c]	not serious	not serious	serious [r]	none	One series of 34 cases reported 38% of patients visiting ED over 1 year of observation. The other series of cases from 2 intervention arms in an RCT reported 61% of 204 patients visiting ED over 5 years.				⊕◯◯◯ VERY LOW	IMPORTANT
Any adverse effects (follow up: 16 days)												
1 [16]	observational studies	serious [c]	not serious	not serious	serious [s]	none	75/173 (43.4%)	-	-	-	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio; OR: Odds ratio

Explanations

a. Studies were not blinded and other risk of bias criteria was suboptimally reported.

b. No events

c. Series of cases; no direct comparison with a control group

d. Studies reported mortality between 4% and 36%; we were not able to explain it with duration of observation, patient age, or severity of disease.

e. Confidence interval does exclude an appreciable benefit with PAP or small and likely negligible difference.

f. CI does not exclude an appreciable benefit or almost no difference.

g. Studies reported the range of resolution of OHS between 1.5% and 62%. We could not explain these differences with either length of follow-up, apparent severity of disease, or mode of ventilation.
h. One study enrolled patients without severe OSA and the effect in this population was smaller but excluding this study would not change the overall estimate. RR among those with severe OSA: 1.27 (95% CI: 1.01 to 1.6) and among those without: 1.07 (95% CI: 0.74 to 1.54). There were some baseline imbalances in the proportions of patients with ESS≤10. The average change from baseline in the proportion of those who had ESS ≤10 among those with severe OSA was 23% more in PAP (NIV or CPAP) group and 7% more in controls (Masa 2015), and among those without severe OSA there was a decrease of 3% in those receiving NIV and did not change in controls (Masa 2016).
i. Study was not blinded
j. Only 33 events
k. We did not lower certainty which was already low and imprecise, but there was some inconsistency that could be explained by the type ove PAP: NIV vs. CPAP. NIV (2 studies): 19.30 m more (95% CI: 0 to 39) and CPAP (1 study): 10 m fewer (95% CI: 32 fewer to 12 more).
l. Assuming the minimal important difference of 20 m, the confidence interval does not exclude an appreciable benefit in in important proportion of patients.
m. One study (Borel 2012) reported that no patient required supplemental O2
n. Only 52 events
o. Only 84 patients; CI does not exclude an appreciable benefit or almost no difference)
p. No events in the PAP group and only 60 patients in total.
q. There were only 23 events total
r. only 13 events
s. Only 75 events

References

1. Masa JF, Corral J, Alonso ML, Ordax E, Troncoso MF, Gonzalez M, et al. Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick study. *Am J Respir Crit Care Med* 2015;192:86-95.
2. Borel JC, Tamisier R, Gonzalez-Bermejo J, Baguet JP, Monneret D, Arnol N, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: A randomized controlled trial. *Chest* 2012;141:692-702.
3. Masa JF, Corral J, Romero A, Caballero C, Barrot E, Terán-Santos J, Alonso-Álvarez ML, Gomez-Garcia T, González M, López-Martínez S, De Lucas P, Marin JM, Marti S, Díaz-Cambriles T, Chiner E, Egea C, Miranda E, Mokhlesi B; on behalf of the Spanish Sleep Network. Noninvasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnea: A randomized clinical trial from Pickwick project. Thorax. 2016 Oct;71(10):899-906.
4. Salturk C, Karakurt Z, Takir HB, Balci M, Kargin F, Mocin OY, et al. Comparison of exercise capacity in copd and other etiologies of chronic respiratory failure requiring non-invasive mechanical ventilation at home: Retrospective analysis of 1-year follow-up. . *Int J Chron Obstruct Pulmon Dis* 2015;10:2559-2569.
5. Tsolaki V, Pastaka C, Kostikas K, Karetsi E, Dimoulis A, Zikiri A, et al. Noninvasive ventilation in chronic respiratory failure: Effects on quality of life. *Respiration* 2011;81:402-410.
6. Priou P, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, et al. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010;138:84-90.
7. Piesiak P, Brzecka A, Kosacka M, Jankowska R. Efficacy of noninvasive mechanical ventilation in obese patients with chronic respiratory failure. *Neurobiology of Respiration Advances in Experimental Medicine and Biology* 2013;788.
8. Palm A, Midgren B, Janson C, Lindberg E. Gender differences in patients starting long-term home mechanical ventilation due to obesity hypoventilation syndrome. *Respir Med* 2016;110:73-78.
9. Perez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vazquez Caruncho M, Caballero Muinelos O, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005;128:587-594.
10. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, et al. Obesity-associated hypoventilation in hospitalized patients: Prevalence, effects, and outcome. *Am J Med* 2004;116:1-7.
11. Ojeda Castillejo E, de Lucas Ramos P, Lopez Martin S, Resano Barrios P, Rodriguez Rodriguez P, Moran Caicedo L, et al. Noninvasive mechanical ventilation in patients with obesity hypoventilation syndrome. Long-term outcome and prognostic factors. *Archivos de Bronconeumologia* 2015;51:61-68.
12. Marik PE, Chen C. The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: Analysis of a large cohort. *Obes Sci Pract* 2016;2:40-47.

13. Jothieswaran A, Mascareno M, Bokhari S, Chaudhry N, Felton TW, Bentley AM. Survival in patients with chronic type 2 respiratory failure: A comparison of obesity hypoventilation syndrome, COPD and overlap syndrome. *Thorax* 2015;Conference: British Thoracic Society Winter Meeting 2015. London United Kingdom. Conference Publication: (var.pagings). 2070 (pp A2172-A2173).
14. Heinemann F, Budweiser S, Dobroschke J, Pfeifer M. Non-invasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. *Respir Med* 2007;101:1229-1235.
15. Castro-Anon O, Perez de Llano LA, De la Fuente Sanchez S, Golpe R, Mendez Marote L, Castro-Castro J, et al. Obesity-hypoventilation syndrome: Increased risk of death over sleep apnea syndrome. *PLoS One* 2015;10:e0117808.
16. Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:1279-1285.
17. Budweiser S, Riedl SG, Jorres RA, Heinemann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *J Intern Med* 2007;261:375-383.
18. Borel JC, Burel B, Tamisier R, Dias-Domingos S, Baguet JP, Levy P, et al. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PLoS One* 2013;8:e52006.
19. Blankenburg T, Benthin C, Pohl S, Bramer A, Kalbitz F, Lautenschlager C, et al. Survival of hypercapnic patients with copd and obesity hypoventilation syndrome treated with high intensity non invasive ventilation in the daily routine care. *Open Respir Med J* 2017;11:31-40.
20. Tabernero Huguet E, Gil Alana P, Arana-Arri E, Citores Martin L, Alkiza Basanez R, Hernandez Gil A, et al. Non-invasive ventilation in 'do-not-intubate' patients in a chronic disease hospital. One year follow-up study. *Revista Espanola de Geriatria y Gerontologia* 2016;51:221-224.
21. Sanchez Gomez JF, Pacheco A, Zamora G, Benitez Moya JM, Valido Morales A, T. MR. Results of non-invasive ventilation in patients with acute hypercapnic ventilatory failure and obesity hypoventilation syndrome (ohs). *Eur Respir J* 2012;40:P2042.
22. Salord N, Mayos M, Miralda RM, Farre A, Carreras M, Sust R, et al. Continuous positive airway pressure in clinically stable patients with mild-to-moderate obesity hypoventilation syndrome and obstructive sleep apnoea. *Respirology* 2013;18:1135-1142.
23. Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani A, Hassaballa HA, et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. *J Clin Sleep Med* 2006;2:57-62.
24. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of cpap versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. *Thorax* 2017;72:437-444.
25. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, Man WD. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2018 Apr 1;197(7):961-963.
26. Masa JF, Mokhlesi B, Benitez I, Gomez de Terreros FJ, Sanchez-Quiroga MA, Corral J, et al. Long-term positive airway pressure therapy in obesity hypoventilation syndrome. The pickwick randomised clinical trial. *Lancet* 2019.

Evidence table E3: Should adults with OHS be treated with CPAP or with NIV?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	noninvasive ventilation (NIV)	continuous positive airway pressure (CPAP)	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: range 2 to 3 months)												
3 [1,2,3]	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	0/147 (0.0%)	0/164 (0.0%)	not estimable	0 fewer per 1,000 (from 17 fewer to 18 more)	⊕⊕◯◯ LOW	CRITICAL
Death (follow up: 5 years)												
1 [4]	randomised trials	serious [c]	not serious [d]	not serious	very serious [e]	none	11/97 (11.0%)	16/107 (14.9%)	RR 0.82* (0.36 to 1.87)	29 fewer per 1,000 (from 85 fewer to 86 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life												
3 [1,2,3]	randomised trials	not serious [a]	not serious	not serious	serious [f]	none	117	109	-	SMD 0.08 SD higher (0.35 higher to 0.19 lower) [g]	⊕⊕⊕◯ MODERATE	CRITICAL
Resolution of hypercapnia (follow up: 2 to 3 months; assessed with: $PaCO_2$ <45 mm Hg at the end of the study)												
3 [1,2,3]	randomised trials	not serious [a]	not serious	not serious	serious [h]	none	48/103 (46.6%)	41/113 (36.3%)	RR 1.29 (0.94 to 1.77)	11 more per 100 (from 2 fewer to 28 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Resolution of hypercapnia (follow up: 5 years; assessed with: $PaCO_2$ <45 mm Hg at the end of the study)												
1 [4]	randomised trials	serious [c]	not serious [i]	not serious	serious [h]	none	40/77 (51.9%)	33/81 (40.7%)	RR 1.28 (0.91 to 1.79)	11 more per 100 (from 4 fewer to 32 more)	⊕⊕◯◯ LOW	CRITICAL
Awake hypoxemia (follow up: range 2 to 3 months; assessed with: change from baseline PaO_2 62-66 mm Hg)												
2 [2,3]	randomised trials	not serious [a]	not serious	not serious	not serious	none	99	91	-	MD 0.21 mm Hg lower (3.1 higher to 3.52 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Awake hypercapnia (follow up: range 2 to 3 months; assessed with: change from baseline $PaCO_2$ 51 to 59 mm Hg)												
3 [1,2,3]	randomised trials	serious [j]	not serious	not serious	not serious	none	117	109	-	MD 1.08 mm Hg lower (0.76 higher to 2.91 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Nocturnal oxygen saturation <90% total sleep time (assessed with: change for baseline 70%)												
1 [3]	randomised trials	serious [c]	not serious	not serious	serious [e]	none	69	64	-	MD 3% higher (14.4 higher to 8.4 lower)	⊕⊕◯◯ LOW	IMPORTANT
Apnea–hypopnea index (AHI) (assessed with: change from baseline 70 episodes per hour)												
1 [3]	randomised trials	serious [c]	not serious	not serious	not serious	none	69	64	-	MD 3 episodes/h more (13.37 higher to 7.37 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Motor vehicle accident - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Daytime sleepiness (assessed with: change from baseline in Epworth Sleepiness Scale (range of scores: 0-24; lower score is better; MID ~2-3 points))[5]												
3 [1,2,3]	randomised trials	not serious [a]	not serious	not serious	serious [k]	none	117	109	-	MD 0.76 points lower (0.71 higher to 2.22 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Resolution of daytime sleepiness (follow up: 2 to 3 months; assessed with: 10 or fewer points on Epworth Sleepiness Scale)												
3 [1,2,3]	randomised trials	not serious [a]	not serious	not serious	very serious [e]	none	73/102 (71.6%)	77/111 (69.4%)	RR 1.04 (0.87 to 1.23)	3 more per 100 (from 9 fewer to 16 more)	⊕⊕◯◯ LOW	CRITICAL
Resolution of daytime sleepiness (follow up: 5 years; assessed with: 10 or fewer points on Epworth Sleepiness Scale)												
1 [4]	randomised trials	serious [c]	not serious [l]	not serious	very serious [e]	none	58/78 (74.4%)	57/80 (71.3%)	RR 1.04 (0.86 to 1.26)	3 more per 100 (from 10 fewer to 19 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mood/depression (follow up: 2 years; assessed with: Beck Depression Inventory; MID: ~5 points; Scale from: 0 to 63)												
1 [5]	observational studies	serious [m]	not serious	not serious	not serious	none	141	84	-	MD 2.9 higher (4.25 higher to 1.55 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Cardiovascular events (composite) (follow up: 5 years)												
1 [4]	randomised trials	serious [c]	not serious	not serious	very serious [e]	none	17/97 (17.0%)	16/107 (15.0%)	RR 1.17* (0.56 to 2.44)	3 more per 100 (from 6 fewer to 18 more)	⊕◯◯◯ VERY LOW	CRITICAL
Exercise and/or functional capacity (assessed with: change from baseline in 6-Minute Walk Distance in meters [MID ~20 to 40 m])												
1 [3]	randomised trials	serious [c]	not serious	not serious	serious [n]	none	69	64	-	MD 26 m more (46.56 more to 5.44 more)	⊕⊕◯◯ LOW	IMPORTANT
No need for daytime supplemental oxygen at the end of the study (follow up: 2 to 3 months; assessed with: PaO_2 >55 mm Hg)												
3 [1,2,3]	randomised trials	not serious [a]	not serious	not serious	serious [f]	none	95/103 (92.2%)	104/113 (92.0%)	RR 1.01 (0.94 to 1.08)	1 more per 100 (from 6 fewer to 7 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
No need for daytime supplemental oxygen at the end of the study (follow-up: 5 years; assessed with: PaO_2 >55 mm Hg)												

1[4]	randomised trials	serious [c]	not serious [o]	not serious	serious [f]	none	74/77 (96.1%)	77/81 (95.1%)	RR 1.01 (0.95 to 1.08)	1 more per 100 (from 5 fewer to 8 more)	⊕⊕◯◯ LOW	IMPORTANT
Quality of sleep												
2 [1,3]	randomised trials	serious [j]	serious [p]	not serious	serious [q]	none	One study found a mean difference in change from baseline in arousal index of 4 fewer arousals per hour (95% CI: 15 fewer to 7 more) favoring NIV. (Masa 2015) Another study found a mean difference in change from baseline in PSQI of 3.67 more points (95% CI: 1.25 to 6.09) also favoring NIV. (Piper 2008)				⊕◯◯◯ VERY LOW	IMPORTANT
Hospitalization												
2 [2,4]	randomised trials	not serious [a]	not serious	not serious	very serious [e]	none	Follow-up 3 months: 3/31 in NIV and 3/29 in CPAP group; RR: 0.94, 95% CI: 0.20 to 4.27. (Masa 2019) Follow-up: 5.2 years: 51/97 in NIV and 48/107 in CPAP group; RR: 1.17, 95% CI: 0.88 to 1.55; risk difference: 8 more per 100, 95% CI: from 5 fewer to 25 more). (Howard 2018)				⊕⊕◯◯ LOW	CRITICAL
Emergency department visit (follow up: 5 years)												
1 [4]	randomised trials	serious [c]	not serious	not serious	very serious [e]	none	58/97 (59.8%)	66/107 (61.7%)	RR 0.97 (0.78 to 1.21)	2 fewer per 100 (from 13 more to 14 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Length of hospital stay												
1 [4]	randomised trials	serious [c]	not serious	not serious	not serious	none	97	107	-	MD 0.19 fewer days per person-year (1.13 fewer to 0.75 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference; MD: Mean difference; PSQI: Pittsburgh Sleep Quality Index; *: Adjusted for age, sex, smoking habits and forced vital capacity.

Explanations

a. One study was not blinded but the results of the studies were consistent.

b. No events among only 311 patients

c. Study was not blinded

d. One recent observational study with a control group (Bouloukaki 2018) observed patients with NIV and CPAP for 2 years and found similar risk of death in both groups, but the results were not adjusted and very imprecise (7/141 with NIV and 4/84 with CPAP, RR: 1.04, 95% CI: 0.31 to 3.46, RD: 2 more per 1,000, 95% CI: from 33 fewer to 117 more).

e. Confidence interval does not exclude an appreciable benefit with either intervention compared to the other.

f. Confidence interval does not exclude a small additional benefit with either intervention compared to the other.

g. One relatively small study reported results as median and IQR -- if this study were not included in analysis the SMD would be 0.01 (-0.28 to 0.29).

h. Confidence interval does not exclude an appreciable additional benefit with NIV or no difference.

i. One recent observational study with a control group (Bouloukaki 2018) observed patients with NIV and CPAP for 2 years and found similar probability of resolution of OHS in both groups, but the results were not adjusted for baseline differences (NIV was used only in those in whom "oxygen desaturation persisted after obstructive apneas and hypopneas had been eliminated with CPAP"): 114/141 (80.9%) with NIV and 70/84 (83.3%) with CPAP; RR 0.97, 95% CI: 0.86 to 1.10; RD: 25 fewer per 1,000, 95% CI: from 117 fewer to 83 more).

j. One study was not blinded and the other did not report the methodology in sufficient detail to assess risk of bias.

k. Assuming that MID would be ~2-3 points, the CI does not exclude an appreciable benefit with NIV or no difference.

l. One recent observational study with a control group (Bouloukaki 2018) observed patients with NIV and CPAP for 2 years and found slightly lower probability of resolution of daytime sleepiness with NIV compared to CPAP, but the results were not adjusted for baseline differences (NIV was used only in those in whom "oxygen desaturation persisted after obstructive apneas and hypopneas had been eliminated with CPAP"): 133/141 (94.3%) with NIV and 84/84 (100.0%) with CPAP; RR 0.95, 95% CI: 0.90 to 0.99; RD: 5 fewer per 100, 95% CI: from 1 fewer to 10 fewer).

m. Results were not adjusted for baseline differences (NIV was used only in those in whom "oxygen desaturation persisted after obstructive apneas and hypopneas had been eliminated with CPAP") and 8% were lost to follow-up.

n. Assuming that MID would be ~20 to 40 m, the CI does not exclude an appreciable benefit with NIV or no difference.

o. One recent observational study with a control group (Bouloukaki 2018) observed patients with NIV and CPAP for 2 years found that the probability of not requiring supplemental O2 was similar in both groups, but the results were not adjusted for baseline differences (NIV was used only in those in whom "oxygen desaturation persisted after obstructive apneas and hypopneas had been eliminated with CPAP"): 137/141 (97.2%) with NIV and 84/84 (100.0%) with CPAP; RR 0.97, 95% CI: 0.94 to 1.01; RD: 3 fewer per 100, 95% CI: from 6 fewer to 1 more).

p. see description of results

q. Only 169 patients which likely does not meet optimal information size.

r. PSQI (Pittsburgh Sleep Quality Index) – range of possible scores from 0 to 21; higher score indicates worse quality of sleep.
s. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, Man WD. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2018 Apr 1;197(7):961-963.

References

1. Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of cpap vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax* 2008;63:395-401.
2. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of cpap versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. *Thorax* 2017;72:437-444.
3. Masa JF, Corral J, Alonso ML, Ordax E, Troncoso MF, Gonzalez M, et al. Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick study. *Am J Respir Crit Care Med* 2015;192:86-95.
4. Masa JF, Mokhlesi B, Benitez I, Gomez de Terreros FJ, Sanchez-Quiroga MA, Corral J, et al. Long-term positive airway pressure therapy in obesity hypoventilation syndrome. The pickwick randomised clinical trial. *Lancet* 2019.
5. Bouloukaki I, Mermigkis C, Michelakis S, Moniaki V, Mauroudi E, Tzanakis N, et al. The association between adherence to positive airway pressure therapy and long-term outcomes in patients with obesity hypoventilation syndrome: A prospective observational study. *J Clin Sleep Med* 2018;14:1539-1550.

Evidence table E4: Should hospitalized adults suspected of having OHS, in whom the diagnosis has not yet been confirmed, be discharged from hospital with or without PAP treatment while awaiting confirmation of the diagnosis?

Certainty assessment							Effect				Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Death (follow up: 3 months)												
5 [1-9]	observational studies	serious [a]	not serious	not serious [b]	very serious [c]	none	Among hospitalized patients with OHS or suspected of OHS who survived to hospital discharge (n=1162), 119 (10%) were discharged home without PAP therapy and 1043 (90%) were discharged home on PAP therapy. At 3 months, 20 out of 119 patients (16.8%, 95% CI 10.6-24.8%) who were discharged without PAP had died as opposed to 24 out of 1,043 patients (2.3%, 95% CI 1.5-3.3%) discharged with PAP (p <0.0001); adjusted odds ratio (OR) 0.16, 95% CI 0.08 to 0.33; p <0.0001; estimated risk difference: 136 fewer deaths per 1,000 patients, with 95% CI from 105 fewer to 152 fewer deaths.[d]				⊕◯◯◯ VERY LOW	CRITICAL
5 [1-9]	observational studies	serious [a]	not serious	not serious [b]	very serious [c]	none	Among patients for whom the data about arterial blood gases were available both at baseline and upon discharge from hospital (n=328) the mortality at 3 months without PAP and with PAP was 9.0% vs. 4.4% (19 events; adjusted OR: 0.48, 95% CI: 0.19 to 1.24; estimated RD: 44 fewer per 1000, from 72 fewer to 19 more) and 14.0% vs. 10.5% at 6 months (38 events).[e]				⊕◯◯◯ VERY LOW	CRITICAL
Resolution of OHS - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Motor vehicle accidents - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Daytime sleepiness - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Cardiovascular events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hospitalization - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; OR: Odds ratio; RD: Risk difference

Explanations

a. Analysis of individual patient data from several single-arm studies or individual arms of comparative studies; we were not able to obtain data from 1 study (Nowbar 2004); we did not perform an individual patient data meta-analysis for this guideline but we assumed that given the scarcity and limitations of the source data the results would be similar and not more certain.

b. This was an indirect comparison across several single-arm studies. We did not lower the certainty of evidence for this reason because it has already been very low and the analysis attempted to account for that (IPD).

c. There were few events in total which do not meet the optimal information size; the confidence interval in the adjusted analysis did not exclude both benefit and small harm.

d. Analysis was adjusted for age, sex and baseline $PaCO_2$.

d. Analysis was adjusted for age and sex.

References

1. Borel JC, Burel B, Tamisier R, Dias-Domingos S, Baguet JP, Levy P, et al. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PLoS One* 2013;8:e52006.
2. Budweiser S, Riedl SG, Jorres RA, Heinemann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *J Intern Med* 2007;261:375-383.
3. Castro-Anon O, Perez de Llano LA, De la Fuente Sanchez S, Golpe R, Mendez Marote L, Castro-Castro J, et al. Obesity-hypoventilation syndrome: Increased risk of death over sleep apnea syndrome. *PLoS One* 2015;10:e0117808.

4. Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:1279-1285.
5. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of cpap versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. *Thorax* 2017;72:437-444.
6. Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: A randomised controlled trial. *Thorax* 2012;67:727-734.
7. Palm A, Midgren B, Janson C, Lindberg E. Gender differences in patients starting long-term home mechanical ventilation due to obesity hypoventilation syndrome. *Respir Med* 2016;110:73-78.
8. Priou P, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, et al. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010;138:84-90.
9. Romero C, Sánchez J, Almadana V, Gómez-Bastero A, Guerrero P, Valido A, et al. Results of noninvasive ventilation in obese patients with acute respiratory failure. *Chest* 2014;145:544A.

Evidence table E5: Should a weight loss intervention or no such intervention be used for adults with OHS?

Table E5A: Laparoscopic adjustable gastric banding (LAGB) compared to intensive nutritional care in patients with OHS [a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAGB	intensive nutritional care	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 3 months)												
1 [1]	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	0/30 (0.0%)	0/33 (0.0%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Resolution of OHS (follow up: 3 years; assessed with: weaning from NIV)												
1 [1]	randomised trials	serious [b]	not serious	not serious [d]	serious [e,f]	none	9/30 (30.0%)	4/33 (12.1%)	RR 2.48 (0.85 to 7.21)	179 more per 1,000 (from 18 fewer to 753 more)	⊕⊕◯◯ LOW	CRITICAL
Apnea–hypopnea index (AHI) (follow up: 1 years; assessed with: change from baseline of 52 episodes/h)												
1 [1]	randomised trials	serious [b]	not serious	not serious	not serious [g]	none	26	30	-	MD 22 episodes/h fewer (6 fewer to 39 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Apnea–hypopnea index (AHI) (follow up: 3 years; assessed with: change from baseline of 52 episodes/h)												
1 [1]	randomised trials	serious [b]	not serious	not serious	not serious [g]	none	22	24	-	MD 13 episodes/h fewer (32 fewer to 6 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Weight (follow up: 1 years; assessed with: change from baseline 130 kg)												
1 [1]	randomised trials	serious [b]	not serious	not serious	serious [e,h]	none	26	30	-	MD 12.9 kg lower (30.2 lower to 4.4 higher)	⊕⊕◯◯ LOW	CRITICAL
Weight (follow up: 3 years; assessed with: change from baseline 130 kg)												
1 [1]	randomised trials	serious [b,i]	not serious	not serious	serious [e,j]	none	22	24	-	MD 15.7 kg lower (36.5 lower to 5.1 higher)	⊕⊕◯◯ LOW	CRITICAL
Adverse effects (follow up: 3 years)												
1 [1]	randomised trials	serious [b]	not serious	not serious	serious [k]	none	6/30 (20.0%) [l]	0/33 (0.0%)	not estimable		⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. components of the nutritional care were not described; all patients received a 1400 kcal/d diet
b. Study was not blinded; other risk of bas criteria was not adequately described.
c. There were no deaths among only 63 patients.
d. There is some uncertainty to what extent this reflects resolution of OHS
e. Confidence interval does not exclude an appreciable benefit or no important difference.
f. Only 13 events.
g. We assumed that even the reduction in 32-39 episodes per hour would still not resolve sleep apnea in patients with a baseline average of 52 apnea episodes per hour.
h. Only 56 patients.
i. 22/66 patients were lost to follow-up at 3 years
j. Only 46 patients
k. Only 6 events.
l. All adverse effects were related to the surgery itself: gastric band repositioning due to dysphagia and gastric band replacement, gastric band removal because of gastric band slippage (3, 4, and 9 years after surgery), gastric ulcer (8 years after surgery), and discovery of gastric cancer (7 years after surgery).
m. Only 30 patients; confidence intervals do not exclude an appreciable benefit with either approach.
n. baseline 12 points
o. Only 30 patients; assuming the MID ~20 m the confidence intervals do not exclude an appreciable benefit in some patients.
p. baseline 165-200 m

Reference

1. Feigel-Guiller B, Drui D, Dimet J, Zair Y, Le Bras M, Fuertes-Zamorano N, et al. Laparoscopic gastric banding in obese patients with sleep apnea: A 3-year controlled study and follow-up after 10 years. *Obes Surg* 2015;25:1886-1892.

Table E5B: Gastric bypass compared to no bariatric surgery in patients with OHS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gastric bypass	no bariatric surgery	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 2 years)												
1 [1]	observational studies	serious [a]	not serious	not serious	serious [b]	none	2/29 (6.9%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Resolution of OHS (follow up: 2 years)												
1 [1]	observational studies	serious [a]	not serious	serious [c]	serious [d]	none	25/29 (86.2%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Awake hypoxemia (PaO_2) (follow up: 2 years)												
2 [1,2]	observational studies	serious [a]	not serious	not serious	not serious	none	Mean change from baseline was 15 mm Hg more (95% CI: 9 to 21) (Sugerman 1986) and 19 mm Hg more (11 to 27) (Sugerman 1988).				⊕◯◯◯ VERY LOW	IMPORTANT
Awake hypercapnia ($PaCO_2$) (follow up: 2 years)												
2 [1,2]	observational studies	serious [a]	not serious	not serious	not serious	none	Mean change from baseline was 10 mm Hg less (95% CI: 7 to 13) (Sugerman 1986) and 10 mm Hg less (95% CI: 6 to 14) (Sugerman 1986)				⊕◯◯◯ VERY LOW	IMPORTANT
Daytime sleepiness (follow up: 2 years)												
1 [1]	observational studies	serious [a]	not serious	not serious	serious [d]	none	"Daytime hypersomnolence disappeared"				⊕◯◯◯ VERY LOW	CRITICAL
Weight (follow up: 2 years)												
2 [1,3]	observational studies	serious [a]	not serious	not serious	serious	none	Average weight loss: - 50 kg (95% CI: 39 to 60) from baseline 155 kg in 30 patients (Sugerman 1986) - 44 kg (95% CI: 33 to 55) from baseline 163 kg in 38 patients (Sugerman 1992)				⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary artery pressure (follow up: 3-6 months)												
1 [2]	observational studies	serious [a]	not serious	not serious	serious	none	Pulmonary artery pressure fell on average 13 mm Hg (95% CI: 5.8 to 20.2) from baseline 36 mm Hg				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference

Explanations

a. Series of cases; no direct comparison with a control group

b. Only 2 events among 29 patients

c. Based on "improved or cured" but definition not provided.

d. Only 29 patients.

References

1. Sugerman HJ, Fairman RP, Baron PL, Kwentus JA. Gastric surgery for respiratory insufficiency of obesity. *Chest* 1986;90:81-86.

2. Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. *Ann Surg* 1988;207:604-613.

3. Sugerman HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am J Clin Nutr* 1992;55:597S-601S.

Table E5C: Biliopancreatic diversion with duodenal switch (BPD/DS) compared to no bariatric surgery in patients with OHS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPD/DS	no bariatric surgery	Relative (95% CI)	Absolute (95% CI)		
Resolution of OHS (follow up: 5-7 years)												
1 [1]	observational studies	serious [a]	not serious	not serious	serious [b]	none	16/16 (100.0%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Series of cases; no direct comparison with a control group

b. Only 16 cases

References

1. De Cesare A, Cangemi B, Fiori E, Bononi M, Cangemi R, Basso L. Early and long-term clinical outcomes of bilio-intestinal diversion in morbidly obese patients. *Surg Today* 2014;44:1424-1433.

Table E5D: Weight loss program compared to nutritional and exercise advice in patients with OHS[a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	weight loss programme	nutritional and exercise advice	Relative (95% CI)	Absolute (95% CI)		
Death (follow up: 3 months)												
1 [1]	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	0/17 (0.0%)	1/20 (5.0%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Quality of life (follow up: 3 months; assessed with: SF-36 mental and physical component scores (scale: 0-100; higher score is better; MID ~5))												
1 [1]	randomised trials	serious [b]	not serious	not serious	very serious [d]	none	SF36 mental: mean difference 3.0 (95% CI: -7.67 to 13.66) (baseline: 42 points) SF36 physical: mean difference: 4.6 (95% CI: -2.28 to 11.55) (baseline: 30 points)				⊕◯◯◯ VERY LOW	CRITICAL
Resolution of hypercapnia - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Awake hypoxemia (follow up: 3 months; assessed with: change from baseline in PaO2 of 62 mm Hg)												
1	randomised trials	serious [b]	not serious	not serious	serious [d]	none	15	15	-	MD 0.38 mm Hg lower (7.5 lower to 6.75 higher)	⊕⊕◯◯ LOW	IMPORTANT
Awake hypercapnia ($PaCO_2$) (follow up: 3 months; assessed with: change from baseline in PaCO2 of 53 mm Hg)												
1	randomised trials	serious [b]	not serious	not serious	serious [e]	none	15	15	-	MD 1.95 mm Hg lower (5.25 lower to 1.2 higher)	⊕⊕◯◯ LOW	IMPORTANT
Nocturnal oxygen saturation <90% [% total sleep time] (follow up: 3 months; assessed with: change from baseline 52%)												
1	randomised trials	serious [b]	not serious	not serious	serious [d]	none	15	15	-	MD 3.6 % higher (6.9 lower to 14.1 higher)	⊕⊕◯◯ LOW	IMPORTANT
Apnea–hypopnea index (AHI) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Motor vehicle accidents - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Daytime sleepiness (follow up: 3 months; assessed with: change from baseline in Epworth Sleepiness Scale (lower score is better; MID ~2-3 points); Scale from: 0 to 24)												
1	randomised trials	serious [b]	not serious	not serious	serious [e]	none	15	15	-	MD 2.1 points lower (4.72 lower to 0.48 higher) [f]	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Exercise and/or functional capacity (follow up: 3 months; assessed with: change from baseline in 6-Minute Walk Distance in meters [MID ~20 to 40 m]))												
1	randomised trials	serious [b]	not serious	not serious	serious [g]	none	15	15	-	MD 9.3 m higher (0.7 higher to 18 higher) [h]	⊕⊕◯◯ LOW	IMPORTANT
Dyspnea (follow up: 3 months; assessed with: change from baseline 4 points in Medical Research Council breathlessness scale (range 1-5; lower score is better))												
1	randomised trials	serious [b]	not serious	not serious	serious [e]	none	15	15	-	MD 0.98 points lower (1.87 lower to 0.08 lower)	⊕⊕◯◯ LOW	IMPORTANT
Weight (follow up: 3 months; assessed with: change from baseline 140 kg)												
1	randomised trials	serious [b]	not serious	not serious	serious [e]	none	15	15	-	MD 11.8 kg lower (22.1 lower to 1.5 lower)	⊕⊕◯◯ LOW	CRITICAL
Mood (follow up: 3 months; assessed with: change from baseline 6 points in Hospital anxiety depression scale (lower score is better; MID ~2-2.5); Scale from: 0 to 21)												
1	randomised trials	serious	not serious	not serious	serious [e]	none	15	15	-	MD 1.1 points lower (2.83 lower to 0.63 higher)	⊕⊕◯◯ LOW	IMPORTANT
Need for daytime supplemental oxygen - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Hospitalization - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Emergency department visit - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; MD: Mean difference

Explanations

a. Weight loss program consisted of motivational session, personalized exercise and dietary plan, monthly review, weekly phone calls/reminders; all patients in both groups received NIV

b. Study was not blinded and stopped early for low accrual, large loss to follow-up, and unavailability of personnel to provide intervention.

c. Only one event among 37 patients
d. Only 30 patients; confidence intervals do not exclude an appreciable benefit with either approach.
e. Only 30 patients; confidence interval does not exclude an appreciable benefit or no important difference.
f. baseline 12 points
g. Only 30 patients; assuming the MID ~20 m the confidence intervals do not exclude an appreciable benefit in some patients.
h. baseline 165-200 m

References

1. Mandal S, Suh ES, Harding R, Vaughan-France A, Ramsay M, Connolly B, et al. Nutrition and exercise rehabilitation in obesity hypoventilation syndrome (nero): A pilot randomised controlled trial. *Thorax* 2018;73:62-69.