

Jeffrey I. Mechanick, M.D.
Clinical Professor of Medicine
Director, Metabolic Support
Division of Endocrinology, Diabetes, and Bone Disease
Icahn School of Medicine at Mount Sinai

President-Elect, American College of Endocrinology
Past President, American Association of Clinical Endocrinologists

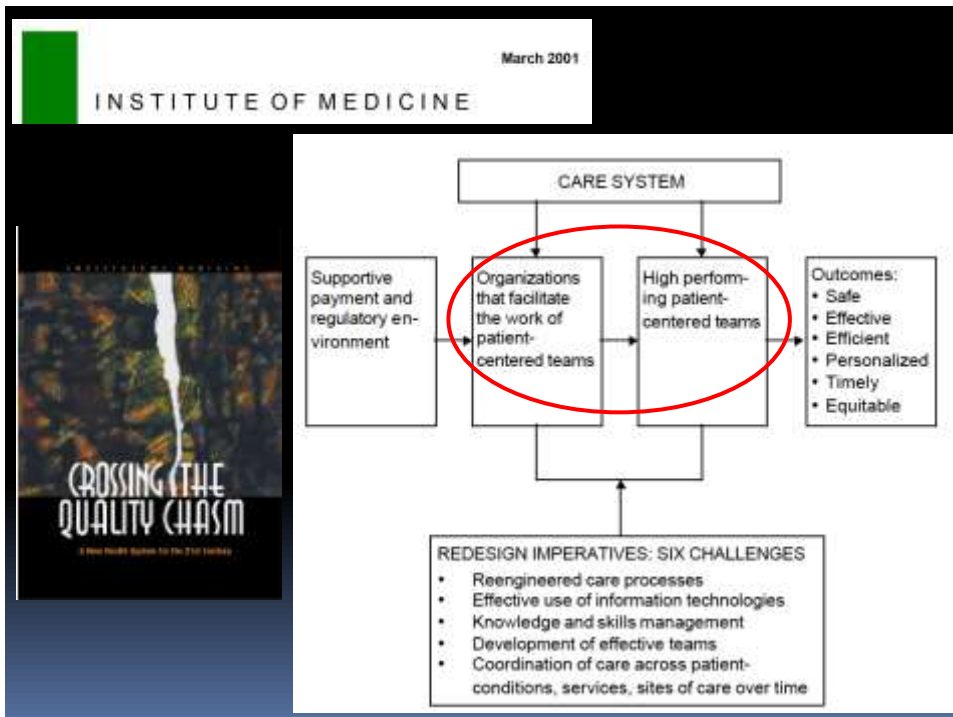
A PATIENT-CENTERED APPROACH FOR INDIVIDUALIZATION OF PHARMACOTHERAPY IN OBESITY CARE

Disclosures

- Received honoraria from Abbott Nutrition International for lectures and program development

Context

- Global epidemic, complex, progressive
- Shortcomings
 - Clinical practice standards
 - Research design
 - Education
- Comprehensive obesity guidelines
- Patient-centered care
- Individualized obesity care
 - Lifestyle
 - Pharmacotherapy
 - Therapeutic procedures



Six Aims for Improvement

- *Safe*: avoiding injuries to patients from the care that is intended to help them.
- *Effective*: providing services based on scientific knowledge to all who could benefit, and refraining from providing services to those not likely to benefit.
- *Patient-centered*: providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions.
- *Timely*: reducing waits and sometimes harmful delays for both those who receive and those who give care.
- *Efficient*: avoiding waste, including waste of equipment, supplies, ideas, and energy.
- *Equitable*: providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status.

Individualized pharmacotherapy

- Part of patient-centered care
- Nuance-based clinical decision making
- Based on co-morbidities
- Should also incorporate transcultural factors
- Limited evidence base
- Optimization process but challenging
- Recommendations: R76 - R119

Pharmacotherapy for Overweight and Obesity

Q7. Is pharmacotherapy effective to treat overweight and obesity?

Q7.1. Should pharmacotherapy be used as an adjunct to lifestyle therapy or alone?

- **R76.** Pharmacotherapy for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone (**Grade A; BEL 1**).

Q7.2. Does the addition of pharmacotherapy produce greater weight loss and weight-loss maintenance compared with lifestyle therapy alone?

- **R77.** The addition of pharmacotherapy produces greater weight loss and weight-loss maintenance compared with lifestyle therapy alone (**Grade A; BEL 1**).
- **R78.** The concurrent initiation of lifestyle therapy and pharmacotherapy should be considered in patients with weight-related complications that can be ameliorated by weight loss (**Grade A; BEL 1**).

Q7.3. Should pharmacotherapy only be used in the short term to help achieve weight loss or should it be used chronically in the treatment of obesity?

- **R79.** Pharmacotherapy should be offered to patients with obesity, when potential benefits outweigh the risks, for the chronic treatment of their disease (**Grade A; BEL1**). Short-term treatment (3-6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence (**Grade B; BEL 1, downgraded due to evidence gaps**).

Table 10. Weight-Loss Medications: Key Clinical Trials, Baseline Characteristics, and Weight-Loss Efficacy (33 [EL 1; RCT]; 34 [EL 1; RCT]; 35 [EL 1; RCT]; 36 [EL 1; RCT]; 37 [EL 1; RCT]) (Note—New Edits From Last Version): (67 [EL 1; RCT]; 68 [EL 1; RCT]; 69 [EL 1; RCT]; 70 [EL 1; RCT]; 71 [EL 1; RCT]) *

Generic Name	Raliuzone ER / Bupropion ER		Liraglutide 3 mg		Lorcaserin		Orlistat		Phentermine/ Topiramate ER			
Brand Name	Contrave		Saxenda		Belviq		Xenical		Qsymia			
Frequency	Oval, BID		w/4Q, QD		Oval, BID		Oval, TID		Oval, QD			
Total Daily Dose	32 mg/360 mg		3 mg		30 mg		360 mg		11 mg / 15 mg	48 mg	82 mg	
	Drug	Control	Drug	Control	Drug	Control	Drug	Control	Drug	Drug	Control	Control
Age (years)	44.4	43.7	45.2	45.0	43.8	43.7	43.2	41.8	51.1	51.0	51.2	
Gender (% Female)	85	85	78.7	78.1	85.5	78.0	79	78	70.0	70.0	70.0	
Baseline Weight (kg)	99.7	99.5	106.2	106.2	100.3	100.5	100.5	101.8	102.4	103.0	103.3	
Baseline Weight (lbs)	108.8	110.0	115.0	114.3	108.9	110.2	n/a	n/a	112.4	113.2	113.4	
Baseline BMI	36.1	36.2	38.5	38.3	36.0	35.9	36.0	36.1	36.2	36.6	36.7	
Weight Loss (% Compliance)	-8.1	-1.8	-9.2	-3.5	-7.9	-4.0	-8.78	-4.26	-9.6	-12.4	-1.6	
Weight Loss (% ITT/LOCF)	-6.1	-1.3	-8.0	-2.8	-5.8	-2.8	-7.94	-4.14	-7.8	-9.8	-1.2	
% Weight Loss (n % ITT/LOCF)	48	16	83.2	27.1	47.2	25.0	50.5	30.7	62	70	21	
10% Weight Loss (n % ITT/LOCF)	25	7	33.1	10.6	22.6	9.7	28.6	11.3	37	48	7	

- **R80.** In selecting the optimal weight-loss medication for each patient, clinicians should consider differences in efficacy, side effects, cautions, and warnings that characterize medications approved for chronic management of obesity, as well as the presence of weight-related complications and medical history; these factors are the basis for individualized weight-loss pharmacotherapy; a generalizable hierarchical algorithm for medication preferences that would be applicable to all patients cannot currently be scientifically justified (**Grade A; BEL 1**).
- **R81.** Clinicians and their patients with obesity should have available access to all approved medications to allow for the safe and effective individualization of appropriate pharmacotherapy (**Grade D**).

Q7.5. Should combinations of weight-loss medications be used in a manner that is not approved by the US Food and Drug Administration?

- **R82.** Combinations of FDA-approved weight-loss medications should only be used in a manner approved by the FDA (**Grade A; BEL 1**) or when sufficient safety and efficacy data are available to assure informed judgment regarding a favorable benefit-to-risk ratio (**Grade D**).

Individualization of Pharmacotherapy in the Treatment of Obesity

Q8. Are there hierarchies of drug preferences in patients with the following disorders or characteristics? (see Figure 5)

Q8.1. Chronic kidney disease

- **R83.** Weight-loss medications should not be used in the setting of end-stage renal failure, with the exception that orlistat and liraglutide 3 mg can be considered in selected patients with a high level of caution (**Grade B; BEL 2**).
- **R84.** The use of naltrexone ER/bupropion ER, lorcaserin, or phentermine/topiramate ER is not recommended in patients with severe renal impairment (<30 mL/min) (**Grade B; BEL 2**).
- **R85.** All weight-loss medications can be used with appropriate cautions in patients with mild (50-79 mL/min) and moderate (30-49 mL/min) renal impairment, except that in moderate renal impairment the dose of naltrexone ER/bupropion ER dose should not exceed 8 mg/90 mg twice a day, and the daily dose of phentermine/topiramate ER should not exceed 7.5 mg/46 mg (**Grade B; BEL 2**).
- **R86.** Orlistat should not be used in patients with, or at risk of, oxalate nephropathy (**Grade C; BEL 3**). Liraglutide 3 mg should be discontinued if patients develop volume depletion, for example, due to nausea, vomiting, or diarrhea (**Grade B; BEL 2**).

Q8.2. Nephrolithiasis

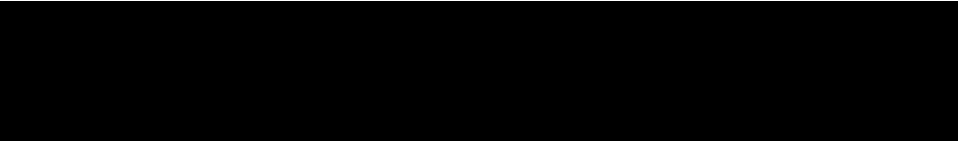
- **R87.** Naltrexone ER/bupropion ER, lorcaserin, and liraglutide 3.0 mg are preferred weight-loss medications in patients with a history, or at risk, of nephrolithiasis (**Grade D**). Caution should be exercised in treating patients with phentermine/topiramate ER and orlistat who have a history of nephrolithiasis (**Grade A; BEL 1**).

Q8.3. Hepatic impairment


- **R88.** All weight-loss medications should be used with caution in patients with hepatic impairment and should be avoided in severe hepatic impairment (ie, Child-Pugh score >9) (**Grade C; BEL 3**).
- **R89.** Dose adjustments for some medications are warranted in patients with moderate hepatic impairment: specifically, the maximum recommended dose of naltrexone ER/bupropion ER is 1 tablet (8 mg/90 mg) in the morning; the maximum recommended dose of phentermine/topiramate ER is 7.5 mg/46 mg daily (**Grade D**).
- **R90.** Clinicians should maintain a high index of suspicion for cholelithiasis in patients undergoing weight-loss therapy, regardless of the treatment modality; in high-risk patients, liraglutide 3 mg should be used with caution; effective preventive measures include a slower rate of weight loss, an increase in dietary fat, or administration of ursodeoxycholic acid (**Grade A; BEL 1**).

Q8.4. Hypertension

- **R91.** In patients with existing hypertension, orlistat, lorcaserin, phentermine/topiramate ER, and liraglutide 3 mg are preferred weight-loss medications (**Grade B; BEL 1, downgraded due to evidence gaps**). Heart rate should be carefully monitored in patients receiving liraglutide 3 mg and phentermine/topiramate ER (**Grade A; BEL 1**). Naltrexone ER/bupropion ER should be avoided if other weight-loss medications can be used since weight loss assisted by naltrexone ER/bupropion ER cannot be expected to produce blood pressure lowering, and the drug is contraindicated in uncontrolled hypertension (**Grade B; BEL 1, downgraded due to evidence gaps**).
- **R92.** Renin-angiotensin system inhibition therapy (angiotensin receptor blocker or angiotensin converting enzyme inhibitor) should be used as the first-line drug for blood pressure control in patients with obesity (**Grade A; BEL 1**).
- **R93.** Combination antihypertension therapy with calcium channel blockers may be considered as second-tier treatment (**Grade A; BEL 1**). Beta-blockers and thiazide diuretics may also be considered in some patients but can have adverse effects on metabolism; beta-blockers and alpha-blockers can promote weight gain (**Grade A; BEL 1**).




Q8.5. Cardiovascular disease and cardiac arrhythmia

- **R94.** In patients with established atherosclerotic cardiovascular disease, orlistat and lorcaserin are preferred weight-loss medications (**Grade A; BEL 1**). Liraglutide 3 mg, phentermine/topiramate ER, and naltrexone ER/bupropion ER are reasonable to use with caution, and to continue if weight-loss goals are met, with careful monitoring of heart rate and blood pressure (**Grade A; BEL 1**). Cardiovascular outcome trials are planned or ongoing for all weight-loss medications except orlistat.
 - **R95.** Orlistat and lorcaserin are preferred weight-loss medications in patients with a history or risk of cardiac arrhythmia (**Grade B; BEL 1, downgraded due to evidence gaps**). Naltrexone ER/bupropion ER, liraglutide 3 mg, and phentermine/topiramate ER are not contraindicated but should be used cautiously with careful monitoring of heart rate and rhythm (**Grade A; BEL 1**).
- 



Q8.6. Depression with or without selective serotonin reuptake inhibitor therapy

- **R96.** All patients undergoing weight-loss therapy should be monitored for mood disorders, depression, and suicidal ideation (**Grade A; BEL 2, upgraded due to high relevance**).
 - **R97.** Orlistat, liraglutide 3 mg, and phentermine/topiramate ER at initiation (3.75 mg/23 mg) and low treatment (7.5 mg/46 mg) doses may be considered in patients with obesity and depression (**Grade A; BEL 1**).
 - **R98.** Lorcaserin and naltrexone ER/bupropion ER should be used with caution in patients with obesity and depression or avoided if patients are taking medications for depression (**Grade A; BEL 1**).
- 

Q8.7. Anxiety

- **R99.** Maximal dose (15 mg/92 mg) phentermine/topiramate ER should be used with caution in patients with obesity and anxiety disorders (**Grade A; BEL 1**).

Q8.8. Psychotic disorders with or without medications (lithium, atypical antipsychotics, monoamine oxidase inhibitors)

- **R100.** Patients with psychotic disorders being treated with antipsychotic medications should be treated with a structured lifestyle intervention to promote weight loss or prevent weight gain (**Grade A; BEL 1**).
- **R101.** Treatment with metformin may be beneficial in promoting modest weight loss and metabolic improvement in individuals with psychotic disorders who are taking antipsychotic medications (**Grade A; BEL 1**).
- **R102.** Caution must be exercised in using any weight-loss medication in patients with obesity and a psychotic disorder due to insufficient current evidence assessing safety and efficacy (**Grade D**).

Q8.9. Eating disorders including binge eating disorder

- **R103.** Patients with overweight or obesity who are being considered for weight-loss therapy should be screened for binge eating disorder and night eating syndrome (**Grade B; BEL 3, upgraded due to high relevance**).
- **R104.** Patients with overweight or obesity who have binge eating disorder should be treated with a structured behavioral/lifestyle program in conjunction with cognitive behavioral therapy or other psychological interventions (**Grade A; BEL 1**).
- **R105.** In patients with overweight or obesity and binge eating disorder, treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, cognitive behavioral therapy, and/or other psychological interventions (**Grade A; BEL 1**).
- **R106.** Structured lifestyle therapy and/or selective serotonin reuptake inhibitor therapy may be considered in patients with obesity and night eating syndrome (**Grade B; BEL 1, downgraded due to evidence gaps**).

Q8.10. Glaucoma

- **R107.** Liraglutide 3 mg, orlistat, and lorcaserin should be preferred weight-loss medications in patients with a history, or at risk of, glaucoma (**Grade B; BEL 2**). Phentermine/topiramate ER should be avoided and naltrexone ER/bupropion ER used with caution in patients with glaucoma (**Grade C; BEL 2, downgraded due to evidence gaps**).

Q8.11. Seizure disorder

- **R108.** Phentermine/topiramate, lorcaserin, liraglutide, and orlistat should be preferred weight-loss medications in patients with a history, or at risk, of seizure/epilepsy (**Grade B; BEL 1, downgraded due to evidence gaps**). The use of naltrexone ER/bupropion ER should be avoided in these patients.

Q8.12. Pancreatitis

- **R109.** All patients with obesity should be monitored for typical symptoms of pancreatitis (eg, abdominal pain or gastrointestinal distress) due to a proven association between these diseases (**Grade A; BEL 1**).
- **R110.** Patients receiving glyburide, orlistat, or incretin-based therapies (glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase 4 inhibitors) should be monitored for the development of pancreatitis (**Grade C; BEL 3**). Glyburide, orlistat, and incretin-based therapies should be withheld in cases of prior or current pancreatitis; otherwise there are insufficient data to recommend withholding glyburide for glycemic control, orlistat for weight loss, or incretin-based therapies for glycemic control or weight loss due to concerns regarding pancreatitis (**Grade D**).

Q8.13. Opioid use

- **R111.** In patients requiring chronic administration of opioid or opiate medications, phentermine/topiramate ER, lorcaserin, liraglutide 3 mg, and orlistat should be preferred weight-loss medications, while naltrexone ER/bupropion ER should not be used (**Grade B; BEL 1, downgraded due to evidence gaps**).

Q8.14. Women of reproductive potential

- **R112.** Weight-loss medications must not be used in pregnancy (**Grade A; BEL 2, upgraded due to high relevance**).
- **R113.** All weight-loss medications should be used in conjunction with appropriate forms of contraception in women of reproductive potential (**Grade A; BEL 1**).
- **R114.** Weight-loss medications should not be used in women who are lactating and breast-feeding (**Grade D**).

Q8.15. The elderly, age ≥ 65 years

- **R115.** Elderly patients (≥ 65 years of age) should be selected for weight-loss therapy involving structured lifestyle interventions that include reduced-calorie meal plans and exercise, with clear health-related goals in mind that include prevention of type 2 diabetes in high-risk patients with prediabetes, blood pressure lowering, and improvements in osteoarthritis, mobility, and physical function (**Grade A; BEL 1**).
- **R116.** Elderly patients with overweight or obesity being considered for weight-loss therapy should be evaluated for osteopenia and sarcopenia (**Grade B; BEL 2**).
- **R117.** Weight-loss medications should be used with extra caution in elderly patients with overweight or obesity (**Grade A; BEL 1**); additional studies are needed to assess efficacy and safety of weight-loss medications in the elderly.

Q8.16. Addiction/alcoholism

- **R118.** In patients with obesity and alcohol or other addictions, consider using orlistat or liraglutide 3 mg (**Grade A; BEL 1**). Lorcaserin (abuse potential due to euphoria at supra-pharmacological doses) and naltrexone ER/bupropion ER (lowers seizure threshold) should be avoided in patients with alcohol abuse, and naltrexone ER/bupropion ER is contraindicated during alcohol withdrawal (**Grade A; BEL 1**).

Q8.17. Post-bariatric surgery

- **R119.** Patients who have undergone bariatric surgery should continue to be treated with an intensive lifestyle intervention (**Grade A; BEL 1**). Patients who have regained excess weight ($\geq 25\%$ of the lost weight) and who have not responded to intensive lifestyle intervention and are not candidates for reoperation may be considered for treatment with liraglutide 1.8 to 3.0 mg or phentermine/topiramate ER; the safety and efficacy of other weight-loss medications have not been assessed in these patients (**Grade D; BEL 3, downgraded due to evidence gaps**).

Figure 5. Preferred Weight Loss Medications: Individualization of Therapy

Figure 5. Preferred Weight Loss Medications: Individualization of Therapy						
KEY: <input type="checkbox"/> PREFERRED DRUG <input type="checkbox"/> USE WITH CAUTION <input type="checkbox"/> AVOID						
CLINICAL CHARACTERISTICS OR CO-EXISTING DISEASES	MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT					
	Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone ER/ bupropion ER	Liraglutide 3 mg	
Diabetes Prevention (metabolic syndrome, prediabetes)		Insufficient data		Insufficient data		
Type 2 Diabetes Mellitus						
Hypertension			Monitor heart rate	Monitor BP and heart rate. Contraindicated in uncontrolled HTN	Monitor heart rate	
Cardiovascular Disease	CAD		Monitor heart rate	Monitor heart rate, BP	Monitor heart rate	
	Arrhythmia		Monitor heart rate, rhythm	Monitor heart rate, rhythm, BP	Monitor heart rate, rhythm	
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data	
Chronic Kidney Disease	Mild (50-79 mL/min)					
	Moderate (30-49 mL/min)		Don't exceed 7.5mg/46mg per day	Don't exceed 6mg/30mg bid		
	Severe (< 30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug metabolites	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion
Nephrolithiasis	Calcium oxalate stones		Calcium phosphate stones			
Hepatic Impairment	Mild-Moderate (Child-Pugh 5-9)	Watch for cholelithiasis	Hepatic metabolism of drug	Don't exceed 7.5 mg/46mg per day	Don't exceed 6mg/30mg in AM	Watch for cholelithiasis
	Severe (Child-Pugh > 9)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Depression			Insufficient safety data. Avoid combinations of serotonergic drugs	Avoid maximum dose: 15mg/52mg per day	Avoid in adolescents and young adults	
				Avoid max dose: 15mg/52mg per day		
Anxiety						
Psychosis	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data	

Binge Eating Disorder			Possible benefit based on reduction in food cravings	Possible benefit based on studies with topiramate	Possible benefit based on studies with bupropion. Avoid in patients with purging or bulimia nervosa	Insufficient data
Glaucoma				Contraindicated, may trigger angle closure	May trigger angle closure	
Seizure Disorder					Bupropion lowers seizure threshold	
Pancreatitis		Monitor for symptoms				Monitor for symptoms Avoid if prior or current disease
Opoid Use					Will antagonize opioids and opiates	
Women of Reproductive Potential	Pregnancy	Use contraception and discontinue should pregnancy occur	Use contraception and discontinue should pregnancy occur	Use contraception and discontinue should pregnancy occur perform monthly pregnancy checks to identify early pregnancy, risk of cleft lip/palate	Use contraception and discontinue should pregnancy occur	Use contraception and discontinue should pregnancy occur
	Breast Feeding	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Age > 65 years *		Limited data available	Insufficient data	Limited data available	Insufficient data	Limited data available
Alcoholism/ Addiction			Might have abuse potential due to euphoria at high doses	Topiramate might exert therapeutic benefits	Avoid due to seizure risk and lower seizure threshold on bupropion	
Fast-Bowel/ Bowel Surgery		Insufficient data	Insufficient data	Limited data available	Insufficient data	Data available at 1.8 - 3.0 mg/day

Conclusions

- Patient-centered care for the patient with obesity incorporates individualized – nuance based – pharmacotherapy
- This approach should optimize care but will require validation compared with standard generalized approaches
- Clinical practice, research, and training should incorporate the principles of individualized obesity care