Effects of Bariatric Surgery on Psychiatric Medications

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Dr. Richard Yanofsky, MD, FRCPC
richard.yanofsky@uhn.ca
Staff Psychiatrist, Toronto Western Hospital, Bariatric Surgery Program
Lecturer, University of Toronto

Name: Dr. Richard Yanofsky - “Canadian Obesity Weekend – May 2022”

Financial Disclosures

(over past 24 months)

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CanMEDS Roles Covered:

Dr. Richard Yanofsky

Canadian Obesity Weekend 2022

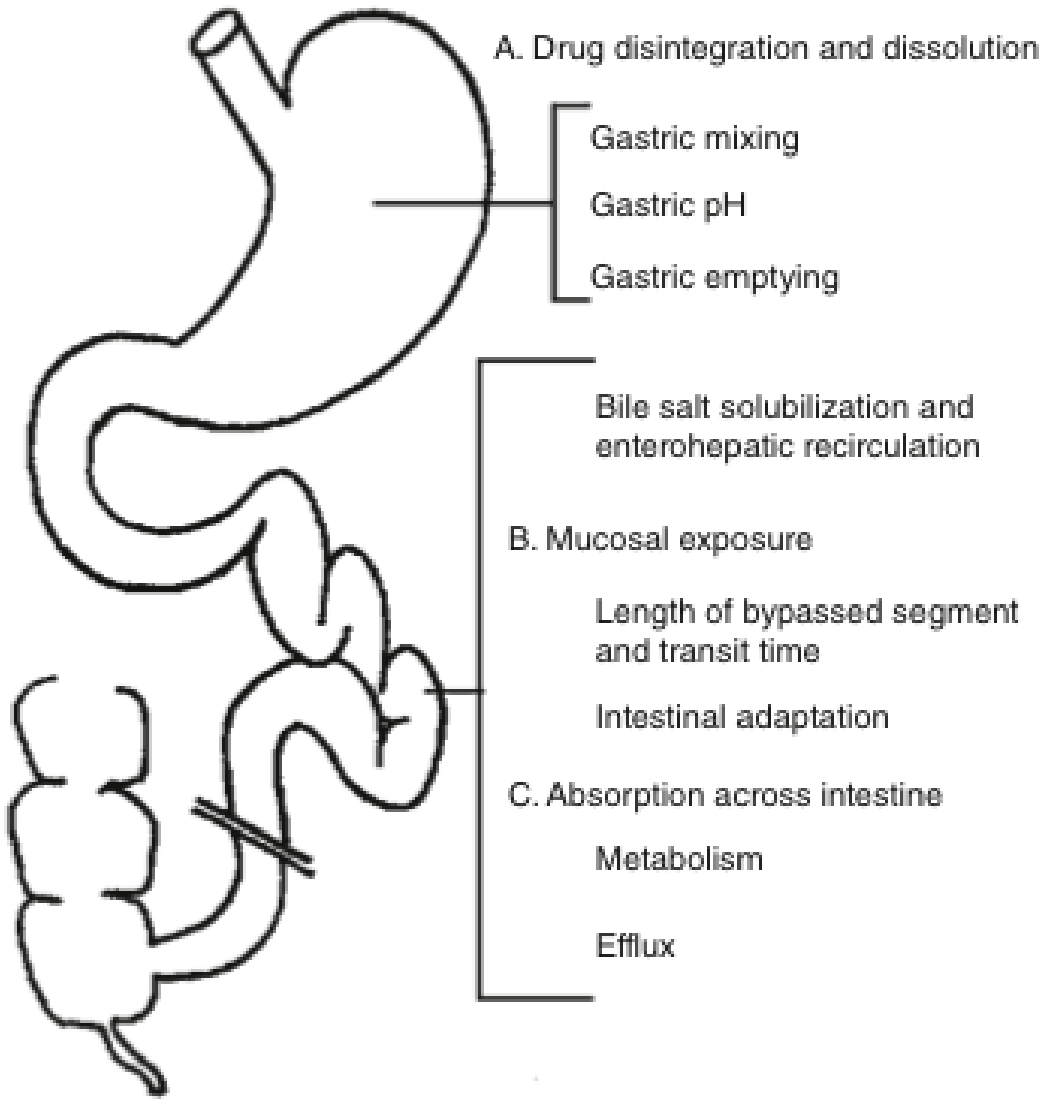
X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	**Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
	Collaborator (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Why have this talk?

- Nearly three quarters of individuals seeking MBS have a lifetime psychiatric history[1]
- About a third of individuals who undergo MBS are on at least one psychotropic medication at the time[2]
- Psychotropic medications are generally continued post-surgically[3]
- Psychiatric medication use is associated with weight gain in general population[4] and may be associated with poorer weight loss outcomes post-RYGB[5]
- MBS confers psychiatric risks and recovery represents a period of psychiatric vulnerability[6]
- MBS may significantly affect pharmacokinetics and bioavailability of psychotropic medications[7] with the specter of toxicity and withdrawal syndromes looming[8-9] over and above the risk of relapse

Pharmacokinetics 101

- What the body does to a drug
- Absorption, Distribution, Metabolism, Excretion
- MBS (RYGB and VSG) both have impact, but RYGB presumably greater overall effect and better understood
- Impact primarily on absorption more than other pharmacokinetic stages
- Optimal absorption of medication is affected by challenges in dissolution, alterations of stomach pH, decreased gastric mixing, delayed emptying, bypass of small intestine, reduced surface area for diffusion[10]



GB GS RYBG BPD JIB

Padwal et al (2010)

Antidepressants

- Best studied psychotropic medications post-MBS and represent largest proportion of psychotropic medications used by individuals who undergo MBS[11]
- SSRI seem to be more affected by MBS than SNRIs[12] (Possible exception Duloxetine)[13]
- Absorption immediately after MBS may decrease by as much as half pre-surgical levels but often return to normal by 6 months[14]
- At 2 years post MBS 1/3 of those taking an antidepressant before surgery are on higher dose or additional agent, and overall proportion of those on antidepressant increased[15]
- Over 10 years of follow-up, patients on antidepressants have a 21% higher risk of new episodes of ≥ 5% weight gain in comparison to those not on antidepressants (from 7 years onward there is no risk of ≥ 5% weight gain)[5]
- The vast majority (90%) of individuals using antidepressants long-term endorse significant improvements of depression[16]

Antidepressants

- Not all antidepressants present same risk to optimal weight loss
- Best option: Bupropion, but many special considerations
- Very good option: Fluoxetine (very good metabolic profile, very long half-life mitigating risk of discontinuation syndrome)
- Less good options: Mirtazapine, Paroxetine, Amytriptyline
- Several agents with less favourable profiles may be used more for sleep or pain (Duloxetine, Paroxetine, Mirtazapine, Amytriptyline), making lower risk options more plausible
- Older medications, less frequently used, less favourable metabolic profile (MAOIs & TCAs), but may indicate treatment refractoriness
- Always be vigilant, maintain high index of suspicion that antidepressant may be contributing to poor weight loss, low threshold to switch
- Theoretical concerns about increased risk of GI bleed and post-operative bleed associated with antidepressants not borne out in MBS literature[17]
- Antidepressant discontinuation symptoms can be mistaken for dumping syndrome or hypoglycemia, highest risk antidepressants are Paroxetine and Venlafaxine[9]

Bupropion

- Excellent metabolic profile (1/2 of Contrave®)
- Very different mechanism from all other antidepressants (not serotonergic)
- No immediate release format in Canada (only SR or XL)
- Advise switch from XL (most common formulation) to SR + dose division if above 150mg + crushed with H2O
- Very bitter and difficult to tolerate when crushed
- Quite stimulating, so second dose at night may cause insomnia (note when using Contrave® as directed as well)
- Possible elevated risks of seizures taken in this manner
- May increase anxiety, so less ideal when anxiety is prominent
- Has benefit in ADHD as well, another common comorbidity with obesity

Antidepressants - weight effect and when to switch

MEDICATION	WEIGHT EFFECT	CONSIDER SWITCH
Bupropion	Negative	Low
Fluoxetine	Minimal	Moderate
Vilazodone	Minimal	Moderate
Levomilnacipran	Minimal	Moderate
Vortioxetine	Minimal	Moderate
Sertraline	Minimal	Moderate
Trazodone	Minimal	Moderate
Imipramine	Minimal	Moderate
Desvelafaxine	Minimal	Moderate
Venlafaxine	Minimal	Moderate

Antidepressants - weight effect and when to switch

MEDICATION	WEIGHT EFFECT	CONSIDER SWITCH
Escitalopram	Minimal	Moderate
Fluvoxamine	Minimal	Moderate
Duloxetine	Minimal	Moderate
Citalopram	Minimal	Moderate
Nortriptyline	Minimal	Moderate
Amitriptyline	Moderate	High
Paroxetine	Moderate	High
Mirtazapine	Moderate	High

Antidepressants – take home

- Need to balance risk of depressive relapse with metabolic and other risks of maintaining or initiating antidepressants post-MBS
- There are a broad range considerations when selecting or switching antidepressant agents, and not all medications are as favourable in leadup to and following MBS
- Some agents should be switched to alternatives preemptively if possible (eg. Desvenlafaxine switch to Venlafaxine if no concerns around S/E), others should be switched to alternate formulations (eg. Bupropion XL to SR), or used with specific administration instructions (eg. Venlafaxine open capsules)
- Most individuals should stay on antidepressant(s) following bariatric surgery and should be monitored closely clinically for signs of relapse, discontinuation syndrome, and insufficient weight loss post-MBS
- Maintain a high index of suspicion and low threshold to change antidepressant agents, especially when less favourable metabolic profile of agent, newer treatment, or less strong indications for use

Mood Stabilizers and Anticonvulsants

- Far less commonly prescribed than antidepressants in individuals pursuing MBS[2], but often more critical to mental health stability, more complicated to manage, and less interchangeable within class than other Rx regimens
- Treatment of Bipolar Disorder divided into phases of illness, and not all mood stabilizers equally effective at every phase
- Most robust and broadly effective treatments across Bipolar spectrum are Lithium and Valproic acid, both of which confer significant metabolic risk and pose challenges in monitoring
- Over three quarters of individuals who take Lithium report weight gain, with an average increase of nearly 10% of baseline body weight[18]
- Weight gain associated with Valproic acid is slightly less than with Lithium but still significant, with about half of individuals who use it reporting weight gain in excess of 4 kg[19]

Lithium

- Narrow therapeutic index - ie. Small window between no effect and toxicity
- Behaves as a salt in the body and as such very sensitive to fluid shifts
- Numerous case reports of Lithium toxicity following bariatric surgery[20,21,22]
- Perioperative period also represents risk due to prescription of liquid diets
- Patients should receive +++ education about monitoring fluid intake and signs of acute and chronic toxicity if stabilized on Lithium and pursuing bariatric surgery
- Lithium prescribers should be engaged directly and should demonstrate willingness to comply with some form Lithium monitoring protocol

Lithium Monitoring Protocol - TWH BSP

https://twhbaricare.wordpress.com/3d-blood-works/

	Recommendations
Pre-Surgery **While Taking Liquid Meal Replacement***	• Weekly lithium levels • Educate patient to drink 2.5-3 L per day (includes Liquid Meal Replacement) • Consider lithium dose decrease if lithium levels approach 1.2mmol/L or increase by > 25% from baseline • Hold and reassess dose if signs of lithium toxicity • Monitor depressive or manic symptoms (consider using standardized scales**)
Post-Surgery **0-6 Weeks Post-Surgery**	• Weekly lithium levels as fluid intake will increase gradually over initial months post surgery*** • Ask about food intolerance and vomiting as it can impact fluid intake • Consider lithium dose decrease if lithium levels approach 1.2mmol/L or increase by > 25% from baseline • Hold and reassess dose if signs of lithium toxicity • Monitor depressive or manic symptoms (consider standardized scales)
Post-Surgery **>6 Weeks Post-Surgery**	• Monitor lithium levels q2weeks until 6 months post-surgery and then proceed to monthly lithium levels until 1 year post-surgery • Ask about food intolerance and vomiting as it can impact fluid intake • After 1 year post-surgery, resume routine lithium monitoring

Note: Lithium levels should be trough levels
* Duration of Optifast or equivalent meal replacement is based upon pre-surgery weight
**Standardized rating scales include the 17-item or 7-item Hamilton Depression Rating Scale or Patient Health Questionnaire-9 for depression and the Young Mania Rating Scale for mania
***Gradual increase from ~1-1.5 L/day to 2-2.5L/day first few months post-surgery

Valproic Acid and Others

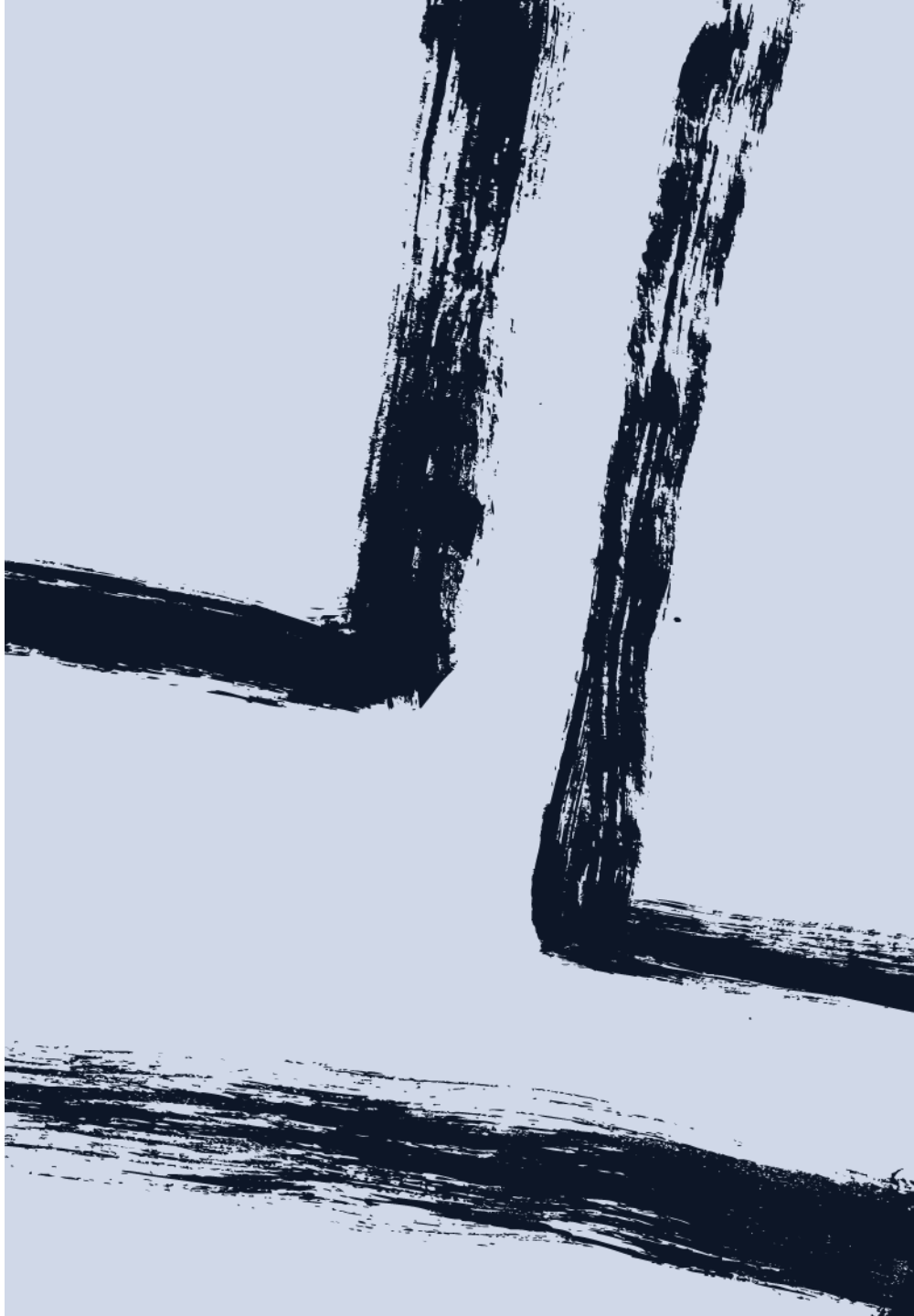
- Toxicity less concerning than with $LiCO_3$ + wider therapeutic window
- Lots of available VPA formulations, including immediate and delayed release capsules, controlled release tablets, suppositories, intravenous and oral solutions, and syrup[23]
- Anecdotal experience with syrup causing dumping syndrome
- Case reports on use of IV VPA to stabilize acute mania in patients with complications following RYGB and poor PO tolerance[24,25]
- Monitoring protocols for VPA also available, see same web address as $LiCO_3$ protocol for TWH BSP VPA monitoring protocol
- Carbamazepine has a low risk of weight gain, Lamotrigine often weight neutral, Topiramate usually associated with weight loss (1/2 of Qsymia® not approved by HC)

Mood Stabilizers and Anticonvulsants

MEDICATION	WEIGHT EFFECT	CONSIDER SWITCH
Topiramate	Negative	Low
Lamotrigine	Minimal	Moderate
Carbamazepine	Minimal	Moderate
Pregabalin	Moderate	High
Gabapentin	Moderate	High
Valproic Acid	High	Moderate
Lithium	High	Moderate

Antipsychotics

- Remain prescribed to a small percent of individuals pursuing MBS[2]
- Significant range of metabolic effects (from minimal to severe) and challenges associated with absorption following surgery for some specific agents
- Prescription rates of SGAP medications has doubled since they were introduced in the 90s, and indications for their use has broadened significantly from schizophrenia, to mood stabilization and even augmentation treatment for depression[26]
- Proliferation of common off label uses including affect regulation in personality disorders, eating disorders, anxiety, and insomnia[26]
- Can be difficult to disentangle indication of use, risk of relapse, suitable alternatives, and metabolic burden when assessing the need for an antipsychotic medication in an individual preparing for MBS



Antipsychotics

MEDICATION	WEIGHT EFFECT	CONSIDER SWITCH
Aripiprazole	Minimal	Moderate
Ziprasodone	Minimal	Moderate
Asenapine	Minimal	Moderate
Lurasidone	Minimal	Moderate
Haldol	Minimal	Moderate
Paliperidone	Moderate	High
Risperidone	Moderate	High
Quetiapine	Moderate	High
Olanzapine	High	High
Clozapine	High	Moderate

Antipsychotics

- Aripiprazole, Brexiprazole, Risperidone, Asenapine: good options, minimal concerns from MBS perspective. Risperidone associated with elevated prolactin, which itself associated with metabolic complications, but also very important medication for many
- Ziprasidone: 500kcal co-ingestion is just not possible pre and acutely post- op. Absorption plummets with decreased kcal co-ingestion (60-90% reduced absorption with 250kcal) [27], and is not able to be made up for by increasing dose[28]
- Lurasidone: 350kcal co-ingestion is closer to attainable. Absorption reduction with decreased kcal co-ingestion is less dramatic than with Ziprasidone (50% dose reduction on empty stomach), and some indication that it may be possible to overcome malabsorption with increased dose[29]

Antipsychotics

- Paliperidone: active metabolite of Risperdione, only avaialbe in ER formulation which poses risk of suboptimal absorption post MBS. Consider switch to Risperidone or switch to LAI of Paliperidone
- Olanzapine: very important and highly effective treatment use in Schizophrenia and Bipolar Disorder. Most metabolically fraught side effect profile save for Clozapine. Lots of formulation options to choose from (no LAI in Canada)
- Quetiapine: most broadly used antipsychotic, with large dose range depending on indication. XR formulation often encountered in clinical practice (switch to IR). Use as hypnotic or anxiolytic should be scrutinized. Consider dividing doses >300mg to optimize absorption (if tolerable, can be quite sedating)

Clozapine

- Lots to consider! But will not be encountered frequently[29]
- Only antipsychotic that works better than all the others, but severe side effect profile limits use
- Will require close collaboration between MBS team, treating mental health team, and pharmacy
- Frequent bloodwork, at minimum monthly to monitor for agranulocytosis
- Clozapine levels not clearly useful to predict response or toxicity, but may be helpful to monitor for possible malabsorption post MBS[30]
- Constipation is common and may be severe or even life threatening in individuals taking Clozapine[31], therefore of particular concern to those also pursuing MBS
- Consider increasing frequency of bloodwork back to qweekly or q2weeks following MBS
- Tobacco use is much higher in individuals living with schizophrenia than in the general population[32], and discontinuation of smoking is required by many MBS programs
- Clozapine is metabolized predominantly by CYP1A2, which is induced by tobacco smoke[33]; there is a possibility of precipitating Clozapine toxicity if dose reduction is not commensurate with cigarette cessation (ideally in range of 30-50% clozapine dose reduction)

General Recommendations

- Avoid controlled release formulations: CR, ER, XL, SR, DR, LA
- Switch to immediate release; if not possible crush or spread beads from capsule; if not possible consider alternative
- Use liquids, SL, ODT when available (even as alternatives to IR formulations)
- Divide dosing if tolerable (can be good strategy if suspect malabsorption but at max HC approved dose)
- Monitor closely, use standardized measurement tools (PHQ9, GAD7, etc), establish baseline, communicate clearly with PCP and mental health teams
- Lab monitoring including blood levels of specific medications
- Educate patient about toxicity and discontinuation syndromes
- Switch to alternative medication if concerns about metabolic profile, challenges with absorption anticipated post-MBS, loose indications for use, and/or good alternatives available
- General predisposition to maintaining psychotropic medications that confer little risk and that an individual has been on for a long time

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Thank-you!!