

# Wyoming Drug Utilization Review

## Post-Bariatric Surgery Effects on Antidepressant Use

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Obesity is a major public health concern and has been recognized as a health epidemic since 1997.<sup>1</sup> Worldwide, this disease affects 1.6 million individuals.<sup>2</sup> Obesity is often treated with pharmacological approach but when these options fail, surgical procedures are warranted.<sup>1</sup> The number of bariatric procedures performed in the U.S. has significantly increased. In 1990, 16,000 procedures were performed annually and have increased to 220,000 procedures since 2009.<sup>2</sup>

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Alongside this disease are medical co-morbidities including sleep apnea, type 2 diabetes mellitus, hypertension, cardiovascular disease and mental health issues.<sup>1</sup> It is reported that between 20-60% of extremely obese persons who pursue bariatric surgery have a psychiatric illness.<sup>5</sup> Depression is one of the most prevalent psychiatric co-morbidities in patients seeking bariatric surgery, yet it is not well understood how antidepressant absorption and efficacy changes after bariatric surgery.<sup>4</sup> About 16-40% of patients receive mental health treatment at the time of bariatric surgery.<sup>5</sup> Despite the prevalence of psychiatric illness in patients seeking surgical treatment, there are no accepted guidelines regarding psychotropic dosing in patients with altered gastrointestinal anatomies from bariatric procedures.<sup>4</sup>

Surgical procedures may be purely restrictive, malabsorptive or a combination of the two.<sup>1</sup> The restrictive procedures leave the small intestine intact, so they are less of a concern when it comes to overall malabsorption of drug, compared to intestinal diversion, which reduce absorption surface area.<sup>2,9</sup> It has been suggested that gastrointestinal transit time could be altered, but more evidence is needed to prove this.<sup>2</sup> Jejunioleal bypass is considered an older, obsolete bariatric procedure which is primarily malabsorptive.<sup>1,5</sup> There are small studies and case reports of pharmacokinetic variabilities, but they are mostly reported in reduced absorption in non-psychoactive agents like digoxin, oral contraceptives, cyclosporine, sulfisoxazole and tacrolimus.<sup>5</sup> There are no data on this specific procedure and its effects on antidepressant use.

The most common surgical procedure for weight loss is Roux-en-Y gastric bypass (RYGB) which accounts for 50% of all procedures and is considered the gold standard in the United States for weight loss in the morbidly obese.<sup>1,5</sup> RYGB is considered both restrictive and malabsorptive procedure in which the proximal stomach is reattached to central small intestine, bypassing the duodenum and 50-70cm of the jejunum.<sup>1</sup> The duodenum is a site for Cytochrome P450 CYP isoenzymes, CYP3A4 and CYP3A5.<sup>2</sup> Drugs metabolized by these enzymes could lead to an increase in bioavailability from the bypass.<sup>2</sup> Keep in mind the antidepressants, citalopram, escitalopram and mirtazapine which are metabolized by CYP3A4, when monitoring therapeutic efficacy or side effects in patients post-RYGB operation.<sup>10</sup>

A small gastric pouch is created in RYGB, which causes an increase in gastric pH due to its separation from the distal regions of the stomach containing acid producing cells.<sup>1</sup> Theoretically, this increase in gastric pH may decrease the solubility of weakly basic drugs and possibly increase drug permeability; more likely affecting drugs that depend on an acidic environment for optimal dissolution.<sup>1</sup> There have been reports of reduced levels in serotonin reuptake inhibitors (SRI) possibly due to reduced gastric acidity post-surgery, which decreases solubility and absorption of the tablet dose form.<sup>3</sup> But the extent of oral drug absorption

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from the stomach is minimal compared to the small intestine, the major site of drug absorption due to multiple levels of the luminal surface, especially in the duodenum and proximal jejunum.<sup>1</sup> Thus, changes in gastric pH are less likely to cause changes in absorption versus changes in intestinal pH.<sup>1</sup>

An in-vitro study of a drug dissolution model was developed to stimulate the gastrointestinal environment of pre-RYGB operative (control) and post-operative RYGB states, examining 22 psychotropic drugs.<sup>5,8</sup> The drugs chosen were common psychiatric medications including the antidepressants amitriptyline, fluoxetine, paroxetine, sertraline, bupropion, venlafaxine and citalopram. The results found 12 of the 22 medications dissolved differently across the two states.<sup>8</sup> Ten of the 12 dissolved more in the pre-operative controlled state and 2 dissolved to a greater degree in the post-operative state.<sup>8</sup> Bupropion was the only antidepressant agent which dissolved to a greater degree in the post-RYGB state.<sup>8</sup> Citalopram and venlafaxine did not differ in dissolution between states.<sup>8</sup> The remaining antidepressants amitriptyline, fluoxetine, paroxetine and sertraline dissolved slightly more in the pre-operative control model.<sup>8</sup> This dissolution data does not predict therapeutic efficacy but serves to provide limited direction of drug absorption and bioavailability.<sup>8</sup>

Along with the potential of alterations in gastric pH impairing drug dissolution and solubility, there are other changes in pharmacokinetic factors which may reduce medication bioavailability and therapeutic effect.<sup>5</sup> Differences in gastric emptying time, changes in volume of distribution and reduced exposure to absorptive mucosal surfaces are all potential factors to consider in the effects of bariatric procedures on pharmacokinetics of antidepressant drugs.<sup>5</sup> Postoperative weight loss may also complicate drug absorption. Rapid weight loss during the first 18 months has been known to alter the volume of distribution of drugs.<sup>3,7</sup> Postoperative bariatric patients can lose more than 100 pounds of adipose tissue.<sup>7</sup> This marked weight loss is more likely to affect lipid-soluble drugs with large volume of distribution such as the antidepressant fluoxetine, which can potentially shift into other compartments.<sup>7</sup> Drug absorption of poorly water soluble or extended release formulations may have inadequate dissolution as well, due to small intestinal transit time shortened by RYGB.<sup>1</sup> Other hypothesized explanations of reduced therapeutic effect of antidepressants after surgery include the malabsorption of tryptophan, a serotonin precursor, and other vitamins

and minerals which serve as enzymatic cofactors in the synthesis of neurotransmitters.<sup>3</sup>

It is challenging to assess the clinical effect of antidepressant drug absorption after the anatomical changes of bariatric procedures because each drug possesses different pharmacokinetics. The impact of these changes depends on characteristic of the drug, which is why effects of bariatric surgery on medication pharmacokinetics appears to be drug specific.<sup>5</sup> Theoretically, the drugs at highest risk of malabsorption are intrinsically poorly absorbed, highly lipophilic or undergo enterohepatic circulation.<sup>5</sup> Antidepressant agents can vary in the extent to which they demonstrate these characteristics.<sup>5</sup>

RYGB patients treated with antidepressants frequently experience exacerbations of psychiatric symptoms postoperatively.<sup>3</sup> The first longitudinal SRI pharmacokinetic in vivo study published in 2012, evaluated the effects of this procedure on absorption of both selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI).<sup>3</sup> The study included several antidepressant medications such as sertraline, venlafaxine, duloxetine, citalopram and escitalopram. The overall results demonstrated a transient reduction in SRI bioavailability 1 month after the surgery but returned back to pre-RYGB levels at 6 and 12 months.<sup>1,3</sup> These results indicate another rationale for close medication monitoring, especially within the first month after surgery as research on this subject matter is still uncertain.<sup>1,3</sup>

Controlling psychiatric symptoms post bariatric surgery is essential for maintaining long term weight loss, safety and quality of life.<sup>3</sup> Procedure and drug specific studies are further warranted to ensure bariatric patients are receiving benefits from drug therapy.<sup>9</sup> Liquid formulations are available for many SRIs and may be considered for safe and effective dosing.<sup>3,4</sup>

*See page 3 for references*

P & T Committee meetings are held quarterly in Cheyenne at Laramie County Community College, 10 am - 1 pm. Please visit the WY-DUR website at [www.uwyo.edu/DUR](http://www.uwyo.edu/DUR) for meeting details. The next meeting is Thursday, August 11, 2016.

## P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on May 11, 2016.

Highlights of this meeting include:

A new vendor, Optum, has been selected for medical case management services, which will continue under the name of WyHealth. The CMS proposed final rule for MACRA has been published. Payment under Medicaid and Medicare will switch to the merit-based incentive payment system (MIPS). The Primary Care Medical Home is recognized as an alternative payment method, which is the only way to bypass MIPS.

Victoza will be limited to a dose of 1.8 mg per day. Lyrica will be limited to 600 mg per day. Suboxone will be limited to 16 mg per day for the first two years and 8 mg per day after two years.

The diagnosis requirement for ADHD in children aged 4 – 17 years will be removed. For those patients who require the diagnosis, the lookback period will be 14 months.

Zepatier will be allowed under current Hepatitis C clinical criteria with an additional requirement for NS5A polymorphism testing.

Prior authorization will be required for use of a benzodiazepine in combination with another benzodiazepine or a narcotic medication.

The proposed prior authorization criteria will be posted for public comment at [www.uwyo.edu/DUR](http://www.uwyo.edu/DUR). Comments may be sent by email to [alewis13@uwyo.edu](mailto:alewis13@uwyo.edu) or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to July 1, 2016.

The next P&T Committee meeting will be held August 11, 2016 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

### References for *Post-Bariatric Surgery Effects on Antidepressant Use*

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P&T Committee Meeting Update**

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