PHARMACY PHACTS

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Extrapyramidal Symptoms: A Review of Symptoms and Management

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Extrapyramidal symptoms (EPS), produced secondary to antipsychotic-induced dopamine blockade, are divided into four distinct symptom clusters: acute dystonia, Parkinsonism, akathisia, and tardive dyskinesia (TD). Although these symptoms can have varying presentations, they are frequently dose related and most closely associated with higher potency dopamine-blockade. High potency antipsychotics that are commonly implicated in the development of EPS include agents such as haloperidol, fluphenazine, perphenazine, risperidone, and paliperidone. In addition to antipsychotics, other medications known to cause movement disorders include antiemetics (droperidol, metoclopramide, and prochlorperazine), lithium, selective serotonin reuptake inhibitors, stimulants, tricyclic antidepressants, and some antiepileptic agents. The risk of EPS development is largely mitigated through conservative dosing and cautious dose titration; however, the potential for EPS development highlights the importance of monitoring by both patients and healthcare providers for the development of these symptoms throughout the course of treatment.

Acute dystonia is defined as a sustained involuntary twisting or muscle contraction, which may present as facial grimacing, oculogyric crisis (deviation of eyes upward or in a lateral direction), laryngospasm, or torticollis (twisting of the neck). Although pain may or may not be present, the patient may experience difficulty with respiration, ambulation, or speech that is often associated with feelings of distress. The onset of acute dystonia is sudden and occurs within several hours to days of exposure to a dopamine-blocking agent. Dystonia may also occur with dose escalation of a dopamine-blocking agent or dose reduction of a concomitant anticholinergic medication. Tardive dystonia may also occur, developing months to years after initiation of a medication and often co-existing with tardive dyskinesia.

Iatrogenic Parkinsonism is characterized by tremors, hypokinesia, muscle rigidity, postural instability, and loss of associated movements. Medication-induced Parkinsonism is often considered a subacute process with a typical onset within three months of medication initiation or dose titration; it is often reversible upon medication tapering/discontinuation.

Akathisia is described as a subjective feeling of restlessness which may manifest objectively through pacing, foot tapping, and shortened attention span. The onset of akathisia is often within four weeks of medication initiation or dose titration, although withdrawal akathisia is also possible during a medication taper. Akathisia is often misdiagnosed as another medical condition (e.g. restless leg syndrome) or as anxiety or agitation secondary to another psychiatric disorder. Literature describes untreated akathisia as a risk factor for treatment non-adherence, increased aggression, and suicidal

thoughts and behaviors, underscoring the importance of persistent monitoring for this EPS symptom cluster.

Finally, tardive dyskinesia presents as abnormal involuntary movements of which the patient is typically unaware. It most commonly affects the orofacial area and tongue (e.g. lateral jaw movements, tongue protrusion, lip smacking) but may also manifest in the extremities or truncal region. The term "tardive" implies a delayed onset of symptoms, which may present months to years following initial exposure to the medication.

The table below describes evidence-based treatment recommendations for the management of each respective EPS symptom as well as possible risk factors that have been identified in the literature.

Extrapyramidal Symptom	***Treatment***	***Possible Risk Factors***
Tardive Dyskinesia	- Discontinuation or dose reduction of offending medication - Discontinue anticholinergic agents - Consider switching agent to a lower potency medication (e.g. quetiapine or clozapine) if clinically appropriate - Consider trial of a dopamine-depleting agent - Consider trial of ginkgo biloba, amantadine, or a benzodiazepine (clonazepam) - Less evidence available for vitamin E, pyridoxine, melatonin, botulinum toxin, zonisamide, and levetiracetam - Consider deep brain stimulation	- Longer duration of exposure to antipsychotic treatment - Higher antipsychotic dosage - Female sex - Postmenopausal women - Advanced age ($\geq$ 50 years) - History of acute extrapyramidal symptoms with antipsychotics - Intermittent antipsychotic treatment - African American race - Head injury and organic brain disorders - Electroconvulsive therapy - Iron deficiency - Alcohol and other substance use disorders - Affective/mood disorder - Concurrent medical conditions (e.g. diabetes mellitus)
Acute Dystonia	- Discontinue offending medication - Administer an anticholinergic agent (diphenhydramine or benztropine)	- High potency antipsychotics - History of electroconvulsive therapy - Male sex - Intellectual disability - Young age - Presence of tardive dyskinesia
Akathisia	- Discontinuation or dose reduction of offending medication - Consider switching to an alternative antipsychotic agent - Consider trial of a beta-blocker (propranolol) or anticholinergic agent	- Advanced age - Affective disorder - Cognitive impairment - Female sex - High potency antipsychotics - High antipsychotic dose - History of akathisia - Iron deficiency - Negative symptoms of schizophrenia - Rapid antipsychotic dose escalation
Iatrogenic Parkinsonism	- Discontinuation or dose reduction of offending medication - Consider switching to an atypical or lower potency medication - Consider addition of an anticholinergic agent (diphenhydramine or benztropine)	- Advanced age - Dementia - Female sex - Acquired immune deficiency syndrome

Effect of Gastric Bypass on Psychiatric Medications

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The potential presence of coexisting psychiatric diagnoses in patients undergoing bariatric surgery may require the use of psychiatric pharmacotherapy. Nearly one third of bariatric surgery patients require the use of a psychotropic medication in the perioperative period, with antidepressants accounting for about half of these prescriptions. Psychiatric decompensation in those who have undergone gastric bypass surgery has been noted in patients requiring psychiatric pharmacotherapy. This can likely be attributed to complications following surgery such as decreased medication absorption, nausea, vomiting, dehydration, and inability to tolerate oral medications. The American Society for Metabolic and Bariatric Surgery's most recent iteration of the clinical practice guidelines for perioperative management of bariatric surgery fails to discuss this potential complication, so there remains a lack of clear clinical guidance surrounding management of psychiatric medications in the setting of gastric bypass surgery.

The flow of medications along the gastrointestinal (GI) tract in patients undergoing gastric bypass surgery will alter pharmacokinetic parameters and efficacy of medications. One of the most common gastric bypass surgeries, the Roux-en-Y (RYGB), involves creation of a gastric pouch to restrict food intake, essentially decreasing the size of the stomach. The jejunum is then divided and attached to the far end of the modified pouch, creating a partial bypass of the duodenum (location of medication absorption). The evasion of various CYP enzymes (including CYP1A2, CYP3A4, CYP3A5, and CYP2D6) by psychoactive medications also occurs. Possible explanations for reduced absorption include markedly decreased gastric acidity, diminished intestinal surface area, increased gastric emptying, and changes to the volume of distribution of drugs. Other complications that result from functional changes to the GI tract include malabsorption of vitamins and minerals that function as enzyme cofactors, especially those of folate and iron. Increased lean body mass percentage and decreased glomerular filtration rate secondary to reduced kidney size may also impact the pharmacokinetic parameters of psychiatric medications. Over time, the intestinal absorptive capacity may be restored through mucosal hypertrophy as the intestine compensates for reduced intestinal tract length.

It is important to properly manage psychiatric medications to ensure a smooth transition following surgery. Because patients undergoing bariatric surgery may experience significant drops in drug concentration of an SSRI or SNRI, it is also important to utilize symptom severity monitoring tools to identify patients with inadequate bioavailability. Strategies to increase drug concentrations in this population could include ordering dosage forms as liquid, crushing pills, opening capsules if appropriate, using immediate-release preparations, dividing the dosage multiple times a day, utilizing transdermal preparations (selegiline), or simply increasing the dose. When applicable, measuring pre-operative therapeutic medication levels may provide a therapeutic efficacy target in the post-operative period should symptom remission occur. Although all medications with a narrow therapeutic index should be monitored carefully, close monitoring of lithium is especially important due to the common post-surgical complication of dehydration and decreased glomerular filtration rate. Table 1 cites estimated absorption rates before and after RYGB surgery for common psychiatric medications.

To actively identify patients requiring therapy modifications, appropriate monitoring tools should be utilized particularly during the first month, as drug concentrations tend to be the most variable during this time period. Additionally, it is recommended to reassess symptoms at 3, 6, and 12 months and

modify the regimen as necessary to optimize symptom control. Although often overlooked, patient education can aid in the identification of post-surgical worsening of psychiatric symptoms. An elevated risk of suicide has been noted in post-bariatric surgery patients compared to non-surgical patients; therefore, education regarding crisis help lines and centers should be readily available for patients. Ultimately, proper communication and collaboration between the pharmacy, interdisciplinary care teams, and patients is essential to ensuring optimal management of this unique patient population.

Table 1. Percent Absorption of Common Psychiatric Medications before and after RYGB bypass surgery

Medication	Pre-op absorption	Post-op absorption
Fluoxetine*	30 %	11 %
Sertraline*	116 %	10 %
Bupropion*	52 %	73 %
Venlafaxine	59 %	59 %
Citalopram	27 %	31 %
Clozapine*	54 %	43 %
Olanzapine*	45 %	38 %
Quetiapine*	53 %	23 %
Risperidone*	64 %	49 %
Ziprasidone*	77%	27%
Methylphenidate	48%	54 %
Lithium Carbonate*	35 %	75 %

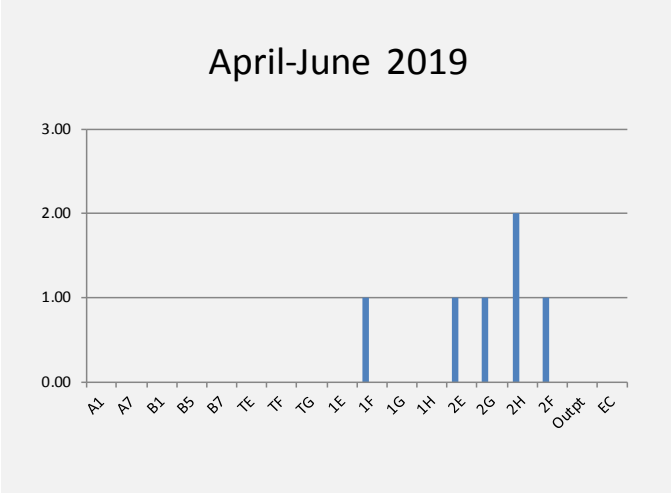
***Statistically significant change in drug bioavailability**

Seaman et al. *Psychosomatics*. 2005;46(3):250-253.

All references available upon request.

Adverse Drug Reactions (ADRs)

Number of ADRs reported



You may report an ADR by calling x3784 or entering the data into the Sunrise Allergies System.

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