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In the Pipeline: Retatrutide, A Triple-Hormone-Receptor Agonist for Treatment of Obesity

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The World Health Organization reports that cardiovascular disease is the primary cause of death worldwide.[1] Poorly controlled diabetes can lead to macrovascular complications that contribute to cardiovascular disease, such as an increased risk of stroke/cerebrovascular disease, coronary heart disease, and peripheral vascular disease. Obesity can further complicate diabetes control, leading to an increase in insulin resistance.[2] Over the past 50 years, obesity rates have almost tripled, and it is a significant contributing factor to increasing cardiovascular risk.[3] Additionally, osteoporosis and certain malignancies, including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and others, can also be associated with obesity.[4] Furthermore, individuals who are overweight are at a higher risk for many noncommunicable diseases, and their risk is directly proportional to their body mass index (BMI).[4] It is projected that by 2030, nearly half of all adults in the United States will be moderate obese (BMI=30-34.9), and almost one-fourth will be severe obese (BMI≥35).[5] Given the link between cardiovascular disease, diabetes, and obesity, the medical community is actively seeking evidence-based treatment options to reduce cardiovascular risk, improve diabetes control, and promote weight loss.

Tirzepatide is a glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist that was approved for weight loss in May 2023. Tirzepatide significantly reduces body weight, decreases HgbA1C, and improves cardiovascular risk factors by lowering blood pressure, triglycerides, and low lipoprotein (LDL).[6] The search for additional evidence-based treatment options continues, with retatrutide, a triple-hormone receptor agonist, currently undergoing Phase 3 clinical trials.

IN THIS ISSUE

MECHANISM OF ACTION

Retatrutide, a triple hormone receptor agonist that works on GLP-1, GIP, and glucagon (GCG) receptors. The drug selectively binds and activates all these receptors, enhancing first and second-phase insulin secretion and reducing glucagon levels. GLP-1 is also a physiological regulator of appetite and caloric intake by delaying stomach emptying. GIP targets the brain by stimulating satiety within the hypothalamus.[7,8] GCG release will help enhance energy expenditure when coupled with GLP-1 and GIP, promoting fat breakdown.[9]

PHARMACOKINETICS

A summary of the pharmacokinetic properties of retatrutide can be found in Table 1. The area under the concentration-time curve during one dosing interval ($AUC_{(0-\tau)}$), maximum observed drug concentration (C_{max}), time at which C_{max} was observed (t_{max}), and half-life associated with the terminal rate constant in the non-compartmental analysis were values that were collected. The plasma concentration of retatrutide $AUC_{(0-\tau)}$ and C_{max} were proportional to the dose range studied. The median time to t_{max} was 12-49 hours after taking the dose. The half-life was approximately six days.[6]

Table 1 | Summary of the Pharmacokinetic Parameters for retatrutide in plasma[6]

	0.5 mg	1.5 mg	3 mg	3/6 mg	3/6/9/12 mg
$AUC_{(0-t)}$ (ng·h/mL)					
Day 1	7180	22600	33800	34500	31800
Week 12	NC	NC	70100	137000	293000
C_{max} (ng/mL)					
Week 1	54.1	228	290	292	265
Week 12	NC	NC	571	1060	2410
T_{max} (h)					
Day 1	48	24	23.8	24	23.95
Week 12	NC	NC	12.17	24	23.95
$t_{1/2}$ (h)					
Week 12	NC	NC	137	135	143
CL (L/h)					
Week 12	NC	NC	0.0428	0.0437	0.041

NC; Not Calculated

Clinical Trials

A phase I, double-blind, placebo-controlled, randomized trial was conducted to investigate the efficacy of retatrutide. The study included subjects with type 2 diabetes who had an HbA1c level of 7.0-10.5%, a BMI of 23-50 kg/m2, and no advanced complications of diabetes. Participants were unable to take any diabetes medication other than metformin. The study randomly assigned participants to receive once-weekly subcutaneous injections of retatrutide, randomized to five ascending dose groups, placebo, or dulaglutide 1.5 mg over 12 weeks. The study enrolled a total of 72 subjects who were predominantly white, with a mean age of 58 years, a BMI of 32 kg/m2, and an HbA1c of 8.7%. Compared to placebo, treatment-emergent adverse events were greater using dulaglutide 1.5 mg and the highest dose of retatrutide (3/6/9/12 mg). The adverse events were primarily gastrointestinal. In the oral glucose tolerance test, dulaglutide and retatrutide 3/3/6 mg and 3/6/9/12 mg decreased glucose $AUC_{(0–2\ h)}$ and plasma glucose levels. Dulaglutide lowered HbA1c by approximately 1.0% from baseline after 78 days, whereas retatrutide showed more considerable reductions, up to ~1.9%. Moreover, retatrutide decreased the glucagon $AUC_{(0–2\ h)}$. Dulaglutide did not significantly affect body weight, but, after 85 days, retatrutide 3, 3/6, 3/6/9/12 mg lowered weight by as much as 9 kg. Retatrutide and dulaglutide were associated with decreased appetite as measured by a visual analog scale. While dulaglutide did not lower LDL, VLDL, or triglyceride levels, larger dosages of retatrutide did. However, retatrutide reduced HDL cholesterol. Retatrutide at large doses also lowered systolic and diastolic blood pressure, although they significantly raised pulse rate.[6] The mechanism behind this reduction is not clear at this time.

A phase 2, multicenter, double-blind, randomized, placebo-controlled trial was conducted to further examine the safety and efficacy of retatrutide. This study involved overweight or obese adults who did not have diabetes but had at least one weight-related condition. A total of 388 adults with a BMI of over 30 or a BMI of 27-30 plus weight-related conditions were enrolled. The subjects were randomly assigned to receive a placebo or dose adjusted to reach one of the four maintenance doses. (1mg, 4mg, 8mg and 12mg). Retatrutide's efficacy and safety were found to be dose-dependent. Subjects treated with retatrutide 12mg for 48 weeks resulted in a mean weight loss of 24.2%. In addition, the weight loss trajectory did not indicate a plateau trough. Similar to the phase 1 trial, the most common adverse events were gastrointestinal-related effects. They were primarily mild to moderate severity and partially mitigated with a lower dose initiation.[9]

As a next step, the TRIUMPH phase 3 program will evaluate the safety and efficacy of retatrutide for chronic weight management, obstructive sleep apnea (OSA), and knee osteoarthritis (OA) in people with obesity and overweight. The trials include:

- TRIUMPH-1: randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety in participants without type 2 diabetes who are obese or overweight, including participants with OSA and OA
- TRIUMPH-2: randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety in participants with type 2 diabetes who are obese or overweight, including participants with OSA
- TRIUMPH-3: randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety in participants with Class II (BMI ≥ 35 kg/m2 and < 40 kg/m2) or Class III (BMI ≥ 40 kg/m2) obesity and established cardiovascular disease
- TRIUMPH-4: randomized, double-anonymized, placebo-controlled trial to investigate the efficacy and safety in participants who are obese or overweight with OA.[11]

Adverse Effects

Gastrointestinal-related side effects were the most frequently reported adverse effect associated with retatrutide. These events include nausea, diarrhea, vomiting, and constipation. Study participants were assigned to the following groups: placebo, 1 mg, 4 mg (initial dose 2 mg), 4 mg (initial dose 4 mg), 8 mg (initial dose 2 mg), 8 mg (initial dose 4 mg), or 12 mg (initial dose 2 mg) or once weekly for 48 weeks. A summary of these events can be found in Table 2. Most gastrointestinal adverse events were mild to moderate in severity and occurred more frequently with the 4 mg starting dose groups rather than the 2 mg starting dose groups.[9]

Drug Interactions

As retatrutide goes through phase 3 trials, more data on drug interaction will become available.

Table 2 | Commonly Reported Adverse Effects[0]

Adverse Effect	Incidence Rate (% reported)						
	Placebo	1 mg	4 mg ID 2 mg	4 mg ID 4 mg	8 mg ID 2 mg	8 mg ID 4 mg	12 mg ID 2 mg
Nausea	11	14	18	36	17	60	45
Diarrhea	11	9	12	12	20	20	15
Vomiting	1	3	12	12	6	26	19
Constipation	3	7	15	6	11	11	16

ID: Initial Dose

Precautions/Contraindications

As retatrutide goes through phase 3 trials precautions/contraindications will become further defined. However, given the exclusion criteria used in the clinical trials thus far, the contraindication will potentially include:

- Family or personal history of medullary thyroid carcinoma (MTC)
- Family or personal multiple endocrine neoplasia syndrome type 2 (MEN-2)
- History of pancreatitis

Dosage, Administration, & Cost

With a half-life of approximately 6 days, retatrutide enables the achievement and maintenance of significant steady-state exposure following once-weekly subcutaneous treatments. Starting doses, treatment doses and maximum doses have not been finalized at this time. The pricing of retatrutide has not yet been determined, however following current trends for other recently approved weight loss medications, the cost may range ~$1,000.[11]

Clinical Implications

Utilizing retatrutide for weight management entails a nuanced evaluation of its clinical implications, featuring both positive and negative aspects. On the positive front, retatrutide exhibits notable enhancements in weight loss and metabolic parameters, including reductions in glucose levels, triglycerides, and LDL cholesterol levels. Furthermore, it demonstrates a positive impact on blood pressure, with an associated increase in heart rate. However, this increase in heart rate occurred up to 24 weeks and then declined. Further research as to the mechanism behind an increase in heart rate and the implications of this may be warranted to ensure safety.

In the context of the phase 2 trial, all participants received lifestyle intervention encompassing regular counseling sessions delivered by a dietitian or qualified healthcare professional, in alignment with current weight loss guidelines such the Dietary Guidelines for Americans.[12] Lifestyle interventions to this extent may not be feasible for patients depending on current health literacy, access to specialists such as dieticians, and time available from healthcare providers to provide extensive counseling. The implications of this lack of access may promotes additional counseling from pharmacists and physicians for all patients to achieve lifestyle modifications when discussing weight loss. Additionally, the cost of the drug may pose an additional accessibility challenge for uninsured and under insured patients or for patient's insurance companies that do not cover the medication.

Retatrutide's predecessors in the GLP-1 RA and GLP-1 RA/GIP class were all initially FDA-approved for Type 2 Diabetes Mellitus. Liraglutide, semagluide and tirzepatide subsequently had secondary approvals under different brand names for weight loss at increased dosages (for liraglutide and semaglutide). Despite this, most insurers no longer cover these medications for weight loss alone due to formulary costs and previous shortages. As a triple agonist, it is likely that retatrutide will be even more expensive than its predecessors and therefore be formulary restricted as well, potentially limiting its use. Cost will therefore be the biggest barrier to market adoption for retatrutide, regardless of patient assistance programs or coupons.

While retatrutide is in its infancy in terms of clinical studies, having gone through phase 1 and phase 2 studies only at this time, their design could be stronger. The active comparator in studies was dulaglutide. Dulaglutide is one of the weakest GLP-1 RA's in terms of weight loss profile, and does not have an independent brand name version FDA-approved for weight loss.[13] Future studies including a weight loss comparison should incorporate liraglutide, semaglutide or tirzepatide when evaluating weight loss outcomes. As phase 3 trials continue, there is an intriguing opportunity to delve into the potential benefits of retatrutide in addressing conditions such as obstructive sleep apnea (OSA) and knee osteoarthritis (OA) among individuals with obesity and overweight.

Despite the encouraging data, retatrutide has not yet been approved, and is still undergoing phase 3 clinical trials. Current studies are constrained by small sample sizes and brief durations, necessitating comprehensive investigations, particularly those employing more robust comparators such as tirzepatide, to elucidate the true value of retatrutide in weight management.

Conclusion

Retatrutide, a novel GIP, GLP-1, glucagon receptor agonist, has promising results with an overall safety and tolerability profile as GLP-1 receptor agonists approved for obesity treatment. As a next step, the TRIUMPH phase 3 program will evaluate the safety and efficacy of retatrutide for chronic weight management, obstructive sleep apnea, and knee osteoarthritis in - people with obesity and overweight.

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CLINICAL PEARL

Over The Counter Weight Loss

Gabriella Perez, PharmD

Given the number of recently approved medications for weight loss, many patients are requesting advice on medications that will promote weight loss. While patients are searching for ways to lose weight they may come across over the counter (OTC) options. Orlistat is used to help individuals in the treatment of obesity and for chronic weight management as an adjunct to reduced-calorie diet and lifestyle modifications.[1] This medication is available as a prescription, Xenical®, and OTC, Alli. Also, it is important to note, Alli is indicated for patients 18 years and older.

Orlistat is a 60 mg capsule taken by mouth three times daily with each main meal containing fat.[1] The dose may be administered up to 1 hour after the meal. Orlistat produces weight loss through inhibition of nutrient absorption, which results in dietary fat absorption inhibition by approximately 30%. Because Orlistat may reduce the absorption of fat-soluble vitamins A, D, E, K, and beta-carotene, it is recommended patients take a daily multivitamin containing these vitamins during therapy, with the multivitamin supplement taken at least 2 hours before or after the administration of orlistat.[1] It is suggested to take the multivitamin at bedtime to ensure proper absorption.[2] Orlistat can produce a mean weight loss of approximately 4% when used when used along with a reduced-calorie, low-fat diet.[1] Examples of these diets include Jenny Craig, Weight Watchers, and DASH.[3]

Patients that take Orlistat may experience side effects such as abdominal pain, increased defecation, flatulence, and headaches.[1] Eating a low-fat diet helps reduce some of these side effects. Orlistat is contraindicated for use in individuals with cholestasis, malabsorption, and pregnancy. To ensure the safe and effective use of orlistat patients should be counseled on the following:

- Each meal must contain fat for it to be effective. However, the patient should be aware that the higher the fat content the higher incidence of GI side effects. It is suggested that about 30% of the meals should be healthy fats. **Table 1** can help guide patients when determining fat intake:

Table 1 | Recommended Daily Grams of Fat[1]

Calories Per Day	1500	1600	1800	2000
Fat Grams Per Meal	16-17	17-18	20	22-23
Fat Gram Limit Per Day	50	53	60	67

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- Skip the dose of orlistat if they are also skipping a meal or the meal contains no fat.

- Orlistat can affect the absorption of other medications and should be separated 2 hours before or after administration of orlistat. Some of these medications are listed in **Table 2.**

Table 2[1]

Cyclosporine	Antiretrovirals	Anti-epileptics	Warfarin
Levothyroxine	Diabetes Medications	Amiodarone	

CLINICAL PEARL

- It is important to note that orlistat effects the absorption of fat-soluble vitamins A, D, E, K, and beta-carotene. It is important for patients taking the medication to take a multivitamin every night before bed.

In conclusion, orlistat offers a potential OTC option for obesity and weight management. To optimize its benefit, patients must be counseled on proper administration and potential side effects.

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CLINICAL CONUNDRUMS

Pocket-Friendly Wellness: Navigating GLP-1 Costs with Comfort

Katie Sanford, PharmD

Glucagon-like Peptide 1 (GLP-1) agonists have been a trending topic for both patients and providers. GLP-1 agonists as a class have been shown to improve blood glucose control, lower A1c, and benefit the cardiovascular system.[1] GLP-1 agonists have also been shown to promote weight loss, with an average weight reduction up to 15% of a patients body weight, during a twelve-month course of these medications.[2] The added benefits of weight loss from these medications goes further than just the impact they can have on an individual's physical appearance. The reduction in weight loss also increases insulin sensitivity, reduces atherosclerosis progression, increases cardiac function, and lowers blood pressure.[3,4] Currently there are many GLP-1 agonists that have an FDA indication for Type 2 Diabetes and are being prescribed for weight loss. Prescribing these medications for off label purposes often results in cost-related challenges, as many insurance companies may not provide coverage when used for weight loss.

Despite coverage issues, GLP-1 agonists continue to be prescribed and in many instances bear a hefty price tag. In fact, it has been estimated that for one patient, Ozempic® (semaglutide) can cost approximately $10,000 a year.5 However, there are several strategies that may be used to help make these medications affordable for patients. Medication manufacturer companies have programs in place to help promote access to many of these medications. For example, patient assistance programs, copay cards, and savings cards.

CLINICAL CONUNDRUMS

NeedyMeds is a tool both patients and providers can use to determine different cost saving strategies for many brand name medications. NeedyMeds is a national nonprofit organization that facilitates connections between individuals and programs designed to assist in covering expenses related to medications and other various healthcare costs. NeedyMeds has several programs listed that may help provide patients with medication assistance. Depending on the type of program, the provider or the patient may apply. NeedyMeds does not process any applications, determine eligibility, or supply medications. In order to determine the programs available for any medications, patients or providers can use the drug search engine. Type in the name of a medication, and a comprehensive list of available programs for that medication will be outlined.[6]

For patients with commercial insurance a copay assistance program may offer GLP-1 agonists at a reduced price, provided the patients meets specific criteria.

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Every copay assistance program may have varying requirements, however in general to receive copay assistance:

- Patients must have a valid prescription for the medication being filled.
- Patient is not eligible if they are enrolled in any type of federal or state health care program with prescription drug coverage (Medicaid, Medicare, Medigap, VA/DoD, Tricare etc.)
- Patient must have commercial insurance
- Patients who pay full cash are excluded from eligibility

Additional information for each GLP-1 agonist copay assistance can be found on each individual medications drug manufactures website. For specific cost saving strategies for each GLP-1 agonist please see Table 1.

Table 1

Medication and Manufacturer	FDA Approved Indications	Cost Saving Strategies
Bydureon® (Exenatide ER) AstraZeneca	♦ Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes[7]	♦ Patient Assistance Program ♦ Mail-In Rebate ♦ Savings Cards/Copay Cards
Byetta® (Exenatide) AstraZeneca	♦ Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes[8]	♦ Patient Assistance Program
Ozempic® (Semaglutide injectable) Novo Nordisk	♦ Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes[9] ♦ Reduction of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular diease[9]	♦ Patient Assistance Program ♦ Savings Cards/Copay Cards
Rybelsus® (Semaglutide tablets) Novo Nordisk	♦ Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes[10]	♦ Patient Assistance Program ♦ Savings Cards/Copay Cards
Trulicity® (Dulaglutide) Eli-Lilly & Co.	♦ Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes[11] ♦ To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes who have established cardiovascular disease or multiple cardiovascular risk factors[11]	♦ Patient Assistance Program ♦ Savings Cards/Copay Cards
Victoza® (Liraglutide) Novo Nordisk	♦ Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes[12] ♦ Reduction of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular diease[12]	♦ Patient Assistance Program

Needymeds. "Healthcare Savings." and “Programs and Services.”, 2023, https://www.needymeds.org/

CLINICAL CONUNDRUMS

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DEVICE ADMINISTRATION

Tips and Tricks: Administering Mounjaro

Madden Stockstill PharmD

Mounjaro (tirzepatide) is as a dual GIP and GLP-1 receptor agonist designed to lower blood glucose levels in individuals with Type 2 Diabetes (T2DM). This once-weekly medication is used in conjunction with lifestyle modifications such as healthy diet and physical activity to enhance outcomes for patients with T2DM. Mounjaro's broad dosing range facilitates collaboration between patients and their healthcare providers in determining the optimal dose, taking into consideration factors such as blood glucose control, adherence, and potential side effects.

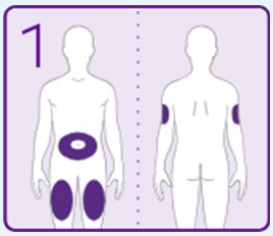
DEVICE ADMINISTRATION

The scheduled dose titration starts off at 2.5mg once weekly, reaching a maximum weekly dose of 15mg. Common side effects associated may include nausea/vomiting, constipation, and indigestion. Notably, Mounjaro carries a black box warning for thyroid C-cell tumors, and its use is contraindicated in patients with acute pancreatitis.[1]

For patients to derive optimal benefits from this medication, it is imperative that healthcare providers possess comprehensive proficiency in both the administration of the medication and the delivery of thorough counseling on proper administration.

Administration Instructions

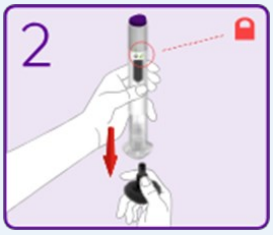
Step 1: Choose your injection site.[1,2]



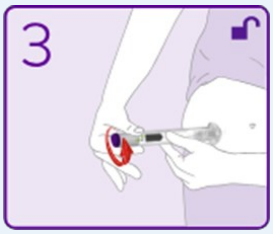
This can be the abdomen, thigh, or back of the upper arm. If the abdomen is chosen, educate patients to make sure injection is at least 2 inches away from belly button. Be sure to advise patients to rotate injection sites to avoid scar tissue build-up.[1,2]

Advise patients to clean the site with an alcohol swab before giving the injection. Educate the patient on correct technique when cleaning the area (i.e. start at the center point and circle out to avoid spreading bacteria back over site). Advise patient to wait about 10 seconds for the alcohol to dry before injecting to avoid burning. [1,2]

Step 2: Remove the gray base cap. [1,2]



Step 3: Place the clear base flat on the cleaned injection site. At the top of the device there is a lock and unlock image, twist to unlock pen.[1,2]

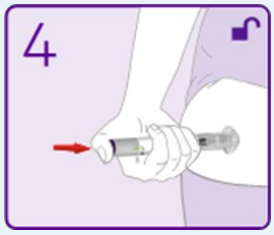


Step 4: Press and hold the purple button at the top of the device for up to 10 seconds. You can ensure the dose has been completely administered by watching the window on the device to see the gray plunger go down. 1,2 It can also be helpful to listen two clicks:

- First click – injection has started
- Second click – injection is complete

Device Administration

Step 4 Continued:



Step 5: Dispose of the pen properly in an FDA-approved sharps container[1,2]

Storage & Disposal

- Mounjaro pens should be stored between 36°F to 46°F (2°C to 8°C) - DO NOT FREEZE[1,3]
- Prior to using patients should check to ensure that the medication is not frozen[1,3]
- Store pens in the original packaging to protect from light.[1,3]
- The medication can remain out of the refrigerate for up to 21 days as long as the temperature does not exceed 86°F (30° C).[1,3]
- To decrease pain and burning with injection, advise patients to take their pens out of the refrigerator and wait to perform the injection until after the pen has reached room temperature.[1,3]
- Mounjaro pens should be disposed of in an FDA-approved sharps disposal container.[1,3]
- If the patient does not have a sharps container, they should use a household container that is made of heavy-duty plastic with a puncture-resistant lid (i.e. laundry detergent container or bleach jug)[1,3]
- Do not place used pens in recycle bins.[1,3]

Clinical Pearls

Mounjaro is unique from other once weekly injectable medications, as it is the first dual GIP and GIP receptor agonist. Mounjaro comes in a one-time use device and has the exact dose needed in each pen. As such, Mounjaro may be a more favorable option for patients who may have lower health literacy, struggle to remember dosing for their medication or have trouble "dialing up" their dose on their own. Another positive aspect of Mounjaro is that this medication may improve adherence to injectable therapy, as it is given once weekly. Lastly, the needle for this device is never visible, which can be helpful for patients who have a needle phobia and would otherwise decline the use of injectable therapy.[1,2,3]

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Personalized Medicine Corner

Cuse of DPYD Pharmacogenetic Testing to Guide Fluoropyrimidine Therapy

Madeline Norris, PharmD

Background

Fluoropyrimidines are antimetabolite medications used for the treatment of solid tumors, often administered in the setting of gastric, head, neck, breast and most commonly, colorectal cancer.[1] The drug class includes 5-fluorouracil (5-FU) and its prodrugs. Fluoropyrimidines are considered to be narrow therapeutic index drugs and, despite their frequent use in oncology, are associated with severe toxicities (grade ≥ 3). Severe toxicities observed after fluorouracil administration include nausea/vomiting, diarrhea, stomatitis and myelosuppression. According to a prospective cohort study of over 1,400 patients treated with standard-of-care capecitabine-based anticancer regimens, life-threatening toxicity following capecitabine treatment is unfortunately common. A total of 16% of patients experienced an early severe toxicity, and 9% of total analyzed patients were hospitalized as a result of a toxicity.[2] The exact cause of these toxicities is unclear, however, it has previously been established that supratherapeutic serum concentrations of 5-FU are significantly associated with treatment-related toxicities of all grades.[3]

5-FU is typically administered intravenously, while its prodrug, capecitabine (Xeloda®), is given as an oral tablet.[4] Capecitabine is metabolized in the liver by carboxylesterase and cytidine deaminase. After conversion to 5-FU, it undergoes the same metabolic pathway as IV 5-fluorouracil. 5-FU undergoes metabolism from multiple sources, with the rate limiting metabolic pathway being dihydropyrimidine dehydrogenase (DPD) conversion of 5-FU to dihydrofluorouracil (DHFU).[5] Patients who have deficient DPD enzyme activity will undergo decreased 5-FU metabolism, and therefore have higher serum concentrations of the compound. It is estimated that 3-5% of Europeans and 8% of African Americans have DPD deficiency when measured by a uracil breath test.[6]

While it is standard practice to dose 5-FU based on body surface area (BSA), this dosing technique still results in highly variable 5-FU serum concentrations.[3] *DPYD* is the gene encoding for the DPD metabolic enzyme, and it is prone to genetic variations that may result in impaired enzyme activity. *DPYD* genetic variations are a probable explanation for inter-individual 5-FU serum concentrations. Patients who have decreased DPD enzyme activity will experience higher 5-FU serum concentrations, and subsequently have an increased risk of treatment-related toxicities.[7]

Pharmacogenetic Results and DPYD Phenotype Definitions

Most pharmacogenetic tests that perform *DPYD* testing focus on 4 of the most well-studied single nucleotide polymorphisms (SNPs) (c.190511G>A (*2A), c.1679T>G (*13), c.2846A>T (rs67376798), and c.1129–5923C>G (HapB3)). These 4 variants are all independently significantly associated with an increased risk of severe fluoropyrimidine-related toxicity.[8] It is estimated that 2% of the total population are carriers of at least 1 of these variants. The frequency is likely highest in Europeans (4.8%), lower in African Americans (0.16%), and very minimal

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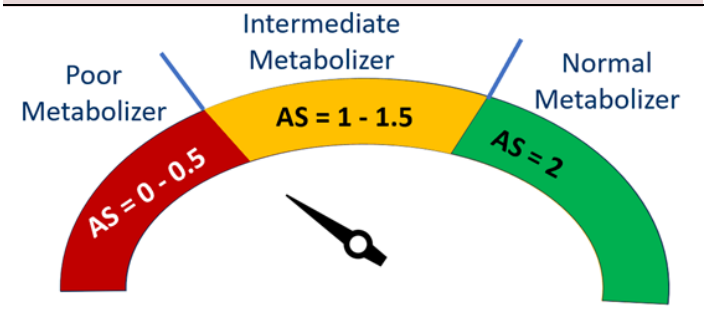
in South Asian patients (0.001%).[9] Some variants are associated with decreased enzyme activity, while others are associated with no enzyme activity. Because of these differing levels of decreased enzyme activity among variants, a method using "activity scores" (AS) based on relative enzyme activity was developed to categorize *DPYD* genotypes, and translate patient diplotypes into phenotypic metabolizer groups (**Figure 1**).[10] Normal metabolizers are patients who carry two normal function alleles and have an AS of 2, intermediate metabolizers have decreased enzyme activity with an AS between 1-1.5, and poor metabolizers have the lowest enzyme activity with an AS between 0-0.5.

Figure 1 | DPYD Phenotype Groups based on Activity Scores



Therapeutic Recommendations and Implementation

There is currently apprehension among oncologists in the United States to recommend *DPYD* testing to help guide fluorouracil dosing in their patients.[9] Previously, the Food and Drug Administration (FDA) and oncology societies in the United States have largely not commented on the need to incorporate *DPYD* pharmacogenetic testing into practice when planning to administer 5-FU and capecitabine. The FDA package labels do not explicitly recommend *DPYD* testing. They do, however, recognize the toxicity associated with DPD deficiency.[1,4] In fact, the FDA has stated that no dose of 5-FU has been proven to be safe for *DPYD* poor metabolizers, but has also stated that there is insufficient evidence to guide a therapeutic dose reduction in *DPYD* intermediate metabolizers. Despite this endorsement of the risk associated with DPD deficiency, the FDA package labels for fluoropyrimidines have failed to comment on whether testing prior to administration is recommended. In 2020, a citizen's petition was submitted to the FDA requesting a revision to the 5-FU and capecitabine package labels.[11] They requested the addition of a boxed warning highlighting the potential dangers of administering 5-FU and capecitabine to patients with a DPD deficiency, and stated that the current language in the labels place the burden on the patient to know and inform their provider of a present DPD deficiency. In December of 2022, the FDA responded and partially accepted the group's recommendation.[12] The FDA revised the language around testing to "more explicitly recommend that prescribers discuss the potential risks of treatment related to DPD deficiency with their patients". Although the agency did not add a boxed warning as requested, they did include a second addition with language encouraging providers to consider *DPYD* testing before initiating capecitabine to reduce the risk of adverse effects. The new updated label still suggests that there is insufficient evidence to guide dose reductions in *DPYD* intermediate metabolizers. This leaves providers with new recommendations to consider ordering and discussing DPYD genetic testing with their patients, but no guidance from the agency on how to use those results once available.

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The Clinical Pharmacogenomics Implementation Consortium (CPIC) provides therapeutic dose recommendations to clinicians wanting to use *DPYD* pharmacogenetic testing to help guide initial fluoropyrimidine dosing.[13] The organization does not comment on the appropriateness or necessity of ordering *DPYD* testing in patients who will receive 5-FU-based regimens, but instead make recommendations under the assumption that pharmacogenetic results are already available. A summary of CPIC's guideline recommendations can be seen in Table 1. Unlike the FDA, the CPIC guidelines provide specific dose reductions in *DPYD* intermediate metabolizers, as well as in poor metabolizers if their use is necessary based on clinical judgement. At the time of publication, CPIC recommended a dose reduction range of 25-50% in *DPYD* intermediate metabolizers with an activity score of 1.5 due to limited evidence. However, since their publication, a large prospective study reported that a 25% dose reduction was insufficient in preventing adverse reactions with 5-FU in patients with an AS = 1.5.[14] This same study showed that a 50% dose reduction was sufficient at reducing the risk of adverse effects. CPIC has revised their guideline recommendations in response to the developing clinical data to more strongly support a 50% dose reduction, rather than 25%, in patients with an AS = 1.5.

Table 1 | Updated CPIC Guidelines for genotype-based fluorouracil dosing

DPYD Phenotype	Dosing Recommendations
Normal Metabolizer (AS =2)	Use label recommended dosage and administration.
Intermediate Metabolizer (AS = 1.5)	Reduce starting dose by 50%.
Intermediate Metabolizer (AS = 1)	Reduce starting dose by 50%.
Poor Metabolizer (AS = 0.5)	Avoid 5-FU based regimens. If clinically necessary, initiate with a strongly reduced dosed (>75%) and early therapeutic drug monitoring.
Poor Metabolizer (AS = 0)	Avoid 5-FU based regimens.

AS = Activity Score

While it has been shown that DPYD genotype-guided fluorouracil dosing reduces the risk of severe toxicities, it is also true that not every patient who carries at least 1 decreased or no function variant will experience this outcome. As a result, it is possible that a patient who would not experience a toxicity at standard doses receives an inappropriate dose reduction. Therapeutic drug monitoring is recommended in patients with decreased DPD activity who have tolerated decreased doses to avoid unknowingly achieving subtherapeutic 5-FU concentrations.

Practical Application/Patient Case:

Use of pharmacogenetic testing to inform genotype-guided dosing has been shown to reduce toxicity associated with 5-FU and capecitabine.[15]

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Practical Application/Patient Case Continued:

With the uptake in testing access, shown feasibility at other large institutions, and improving insurance coverage for testing, it is not unlikely that you may encounter a patient with *DPYD* results available, like the one below, being initiated on a 5-FU-based chemotherapy regimen.[16,17]

PG is a 53-year-old female being initiated on a mFOLFOX6 (5-FU, leucovorin, and oxaliplatin) regimen for treatment of colorectal cancer. Pharmacogenetic testing was ordered prior to treatment initiation to help guide 5-FU dosing.

Standard 5-Fluorouracil Dosing:

400 mg/m2 bolus on day 1, followed by 2,400 mg/m2 over 46 hours (as a continuous infusion) every 2 weeks until disease progression or unacceptable toxicity occurs.

Pharmacogenetic Results:

DPYD c.775A>G / c.1129–5923C>G (HapB3) – Intermediate Metabolizer (AS = 1.5)

Genotype-Based Recommendations:

Based on CPIC's updated guidance, an initial 50% dose reduction should be used for 5-FU in patients with a *DPYD* diplotype equating to an activity score value of 1.5. Continue to titrate based on presence of toxicity and therapeutic drug monitoring when available. Dose should be increased in subsequent cycles if the patient experiences no or tolerable adverse effects in the first 2 cycles, or it is found that the patient has subtherapeutic concentrations.

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On Clinical Decision Support:

Bradley T Hall PharmD

Shortcomings of a Promising Tool

The promise of clinical decision support (CDS) has been to revolutionize patient care through the delivery of timely, patient specific recommendations that are clinically appropriate and practically actionable.[1] However, in recent years, that promise has been threatened by the burden these tools have placed on clinicians.

Since the HITECH Act of 2009, the Meaningful Use program has pushed healthcare systems to enact a wide range of electronic health record functionalities, including CDS. While the initial intention of this law was to improve healthcare coordination and reduce medical mistakes, it is now becoming clear that many of the interruptive alerts implemented with this push have the

potential for just the opposite.

A systematic review in 2020 found that 46.2% to 96.2% of interruptive alerts are overridden.[2] That's a staggering number considering most overridden alerts should be interpreted as the CDS tool adding burden to clinician instead of benefit. Many clinicians are aware of this frustrating burden that non-actionable, inaccurate, poorly timed, or repeated alerts can place on their practice. Distinguishing irrelevant CDS alerts from useful ones wastes clinicians already stretched time and places an unnecessary cognitive burden on them. This "alert fatigue", as it has been coined, threatens to desensitize clinicians after repeated exposure to alerts, resulting in declining responsiveness which can increase the chance that a clinician misses when the CDS alerts them to a care concern accurately.[3]

The burden from poorly built CDS has resulted in a growing number of clinicians, including those in primary care, to feel like the use of CDS causes greater harm than it does good. If fact, some studies support this idea, finding no benefit from primary care CDS tools on outcomes such as morbidity and mortality.[4,5]

While CDS may seem hopeless altogether, other studies have found benefit. A systematic review from 2023 found that primary care providers (PCPs) valued CDS for which they were trained and perceived to be useful. It also found that they appreciated CDS when it was well integrated into their clinical workflow, and provided relevant and reliable recommendations.[6,7] And while PCPs viewed CDS as a net increase in their workload, they largely agreed on the benefit of CDS, the potential to improve quality of care, particularly for preventive care.[7]

Regardless of your stance on CDS, the reality is that this technology is not going away. The question then becomes, how to best address the challenges presented by it.

Strategies to Address the Challenges of CDS

Implement the right type of CDS tool

An interruptive alert is the classic and familiar tool used to convey CDS to clinicians. While these alerts represent a critical type of CDS, it is important to wisely limit them to decisions that are most appropriate given the context. In many cases, passive CDS tools such as an order set, form, or template can produce the desired outcome without placing a great burden on clinicians. Healthcare organizations should consider these alternative options when implementing CDS.

Consider Clinical Workflow

An otherwise well-made CDS tool can be rendered burdensome if not placed properly in a clinician's workflow. CDS should appear to providers at times and locations in which they can act out on the appropriate recommendations. For successful CDS, end-users of the intervention must be engaged to identify optimal workflow fit with the tool.

Optimize Alert Design

Displaying information in a confusing, cluttered, or unhelpful manor results in clinicians having difficulty interpreting CDS. Iterative usability redesign processes evaluating end-user thoughts have been shown to improve the usability of many CDS tools.[8] While all CDS design cannot be evaluated using such a rigorous process, healthcare organizations should use heuristic principles, such as Nielson 10 heuristic principles, when design CDS interventions.[9]

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Keep Content Current

CDS is only as effective as it is accurate. While many CDS tools are implemented with accurate information, over time they become out of date due to a lack of planning for maintenance. Healthcare organizations need to ensure that once CDS tools are built, responsible parties are assigned to maintain the clinical content of these tools. The also should consider when implementing new CDS is unfeasible due to maintenance concerns.

Establish Metrics and Methods to Evaluate CDS Success

Too many CDS interventions are implemented with no strategy or system for obtaining information on its success. In some cases, this is due to incomplete or inaccurate data being all that's available. For this, healthcare organizations should continue expanding the amount of accessible high-quality data. Healthcare organizations should also establish common metrics to assess CDS success with the reliable data available to them now, and consider the value of CDS implementations that cannot be reliable measured.

Concluding Remarks

CDS can be a great benefit or a frustrating burden for clinicians. Clinical informaticists will continue to work on maximizing the benefits and minimizing the burdens of CDS, however, without involvement from clinical end-users, CDS will never fulfil its original promise. I would encourage clinicians reading this article to look for ways they can take an active role in shaping the CDS at their practice site. This could mean joining your health system's CDS governance group to frame broad scale CDS guidance, or simply taking time to provide feedback to CDS implementers. After all, you are the one who will use it.

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