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DISTRICT OF COLUMBIA COLLEGE OF CLINICAL PHARMACY

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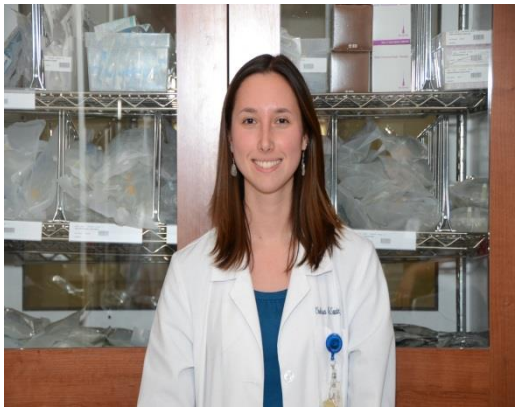
An independent chapter of the American College of Clinical Pharmacy, the DC-CCP is dedicated to improvements in pharmacotherapy practice, education, and research in the District of Columbia, Maryland, and the Commonwealth of Virginia

PRESIDENT'S LETTER



As a member of DC-CCP for the past five years, I am honored to start my term as president of the organization. It has been exciting to see the tremendous amount of growth in the organization throughout the years, and I look forward to continuing on that path during the upcoming year. Thanks to the leadership of the founding members and years past, DC-CCP has grown into a sustainable group spanning the District of Columbia, Maryland, and Virginia. I look forward to seeing the continued expansion of the group as we build upon the numerous relationships and networking opportunities that our past leadership and students have established.

We are anticipating a variety of quality networking and education activities this year, as well as continuing our advocacy efforts in our nation's capital. We plan to provide educational opportunities to students, residents, and clinical pharmacists though our annual CE forum as well as exploring the option of webinars to reach out to a larger geographical audience. I hope to see our strong student involvement grow as we continue to offer networking, mentorship, and residency preparation sessions.

DC-CCP depends upon our active members to support the growth of the organization. I encourage all students, residents,

and pharmacists who wish to get involved to contact me directly or sign up through our recently re-designed website at http://dcccp.wildapricot.org. There are a number of ways to get involved, including committee participation, event planning, attending our annual Advocacy Day, newsletter contributions, mentorship, peer review, and more!

A sincere thanks goes out to our recent past leadership, committee chairs, and active members who continue to be involved in DC-CCP. I look forward to serving as your president, and I am excited for another successful year for DC-CCP.

Chelsea McSwain, Pharm.D., BCPS, BCCCP

DC-CCP President

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CONGRATULATIONS TO THE NEW 2018 DC-CCP OFFICERS!

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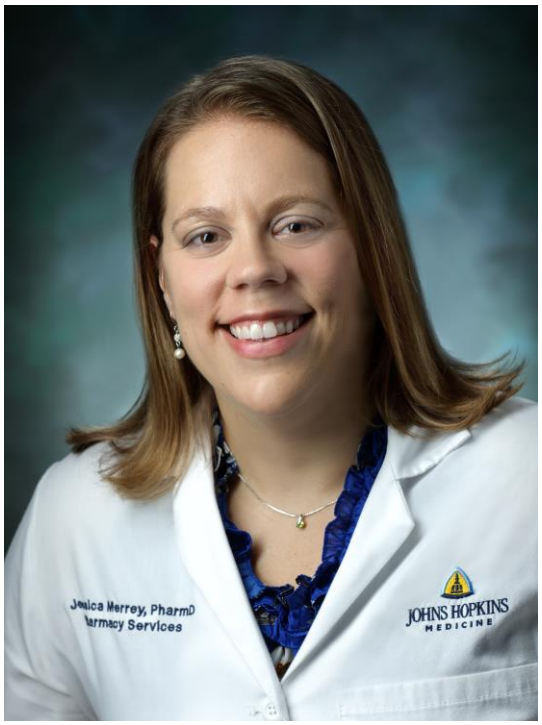
MEMBER SPOTLIGHT

Jessica Merrey Awarded the 2017-2018 Richard Parrish Lecture Award



The Richard Parrish Lecture Award is DC-CCP's highest distinction, and is awarded annually to an individual who exemplifies leadership in clinical pharmacy, by providing significant and sustained contributions in or for clinical pharmacy at the regional or national level. The sixth annual Richard Parrish Lecture Award was presented to Dr. Jessica Merrey, PharmD, BCPS.

Dr. Merry graduated pharmacy school from The Medical University of South Carolina then completed a PGY-1 residency with emphasis in Primary Care at the Ralph H. Johnson VA Medical Center in Charleston, South Carolina. She currently works at The Johns Hopkins Hospital as a clinical pharmacy specialist in ambulatory care and anticoagulation management, a position she has held since 2008. With her passion for care in the elderly population, she currently serves the Geriatric Specialty Council for the Board of Pharmacy Specialties. As a member, she served as president-elect and president of DC-CCP from 2012-2014. Congratulations Dr. Merry!

Angeo Rey Belen Awarded the 2017-2018 Student Leadership Award

This year DC-CCP presented the first Student Leadership Reward to Angeo Rey Belen, a third-year student at the University of Maryland School of Pharmacy. As a student, Angeo has been actively involved in local and regional activities of ACCP as well as other student organizations. This past year Angeo served as DC-CCP Student Communications Chair and his primary role included maintaining the DCCCP social media pages. He was also involved in developing the DC-CCP mentorship series, a mentorship opportunity available to all students in DC-CCP regions. He currently serves as the VP of ACCP-SCCP, where he collaborated with other students to form the Residency Prep Series at the University of Maryland School of Pharmacy. Angeo continues to serve a student role model by staying actively involved in many student organizations.

DC-CCP Residency Series Events Update

Jessica Szatkowsi, Pharmacy Student (Shenandoah University)

On February 15th, a panel of PGY2 residents met at the University of Maryland, Baltimore School of Pharmacy for the second event in the DC-CCP Residency Series. Students from Howard University, NDMU, Shenandoah, and University of Maryland Baltimore were able to view the event in person or via Facebook Live : https://www.facebook.com/shenandoahACCP/videos/1835888033375046/.

The PGY2 residents who shared their wisdom with the students were Drs. Chelsey Song, Matthew Yacobucci, and David Choi from Johns Hopkins and Drs. Jacqueline Chirico and Allie Wasik from the University of Maryland Health System. Pearls offered to the students during the forum included guidance on choosing electives, looking for a PGY1 that would prepare for a PGY2, and discussion about post-residency careers.

Advocacy Day 2018

Amanda Hom, Pharmacy Student (University of Maryland, Baltimore)

About 40 pharmacy students attended from UMD, Shenandoah, and VCU. Students met with offices of Senators from Maryland, VA, PA, and WV as well as Rep. Comstock who represents the Winchester area. It was a great success on a beautiful day!

Investigating Incidence, Monitoring, and Management of Psychiatric Medication Withdrawal: A Literature Review

Mudit Verma, PharmD Candidate 2018, University of Maryland School of Pharmacy

Little information is available regarding medication discontinuation and the resulting adverse withdrawal effects[1]. Recently, the Institute for Safe Medication Practices (ISMP) published a "QuarterWatch" report focusing on medication withdrawal among seven medication classes: (1) antipsychotics (2) antidepressants, (3) anticonvulsants, (4) anxiolytics, (5) hypnotics, (6) neuropathic pain medications, and (7) opioids[2].
However, medication withdrawal symptoms classification is determined primarily based on the neurotransmitter that the medication class notably affects. The quarterly report identified the leading symptoms of psychoactive drug withdrawal as nausea, dizziness, electric shock-like sensations, insomnia, and anxiety. Notably, "QuaterWatch" also reported that the prescribing information underestimates the severity, likelihood, and duration of withdrawal effects. Overall, the focus of this review will be withdrawal signs, symptoms, monitoring and management of antipsychotics, SSRIs, and benzodiazepines.

Regarding antipsychotics, discontinuation syndromes are the primary manifestations of adverse withdrawal effects[1,3]. Neuroleptic Malignant Syndrome upon medication discontinuation is most prevalent with clomipramine, clozapine, haloperidol, and lithium of pharmacokinetic properties such as increased half-life during a prolonged duration of therapy[4]. Risperidone and olanzapine confer the highest risk for serotonin syndrome upon discontinuation[1].

SSRIs are another pertinent medication class concerning withdrawal as a result of discontinuation. Dizziness is the most common characteristic of SSRI withdrawal syndrome[6]. SSRI withdrawal can also lead to symptoms across an array of organ systems such as flu-like symptoms, gait instability, gastrointestinal discomfort, fatigue, paresthesia, visual changes, auditory hallucinations, confusion, and amnesia[7]. Patients who abruptly discontinued sertraline notably experienced orthostatic hypotension[8]. Paroxetine discontinuation had a higher frequency of withdrawal symptoms relative to other SSRIs[7]. Lastly, discontinuation of escitalopram leads to increased dreaming, trouble sleeping, nervousness, anxiety, irritability, as well as sudden worsening of mood[7]. Withdrawal effects of SSRIs can be mitigated with appropriate tapering strategies.

SSRI-induced neonatal withdrawal syndrome is another concern in pregnant mothers regularly taking SSRIs. Infants experience consequent withdrawal symptoms after birth since the infants are no longer receiving SSRI exposure through the mother's bloodstream[9]. Cases of SSRI-induced neonatal

withdrawal syndrome have been reported among infants whose mothers were taking paroxetine, fluoxetine, sertraline, and citalopram[9]. Newborns perinatally exposed to SSRIs or SNRIs based on the mother's treatment are mostly healthy, but treatment for those that experience withdrawal syndromes is primarily supportive care based on specific symptoms[11]. Algorithms regarding treatment of neonatal abstinence syndrome convey that phenobarbital can be used to treat severe non-opioid abstinence syndromes and morphine can be used to treat opioid abstinence syndromes[10].

Withdrawal Monitoring & Management

Various clinical assessment tools are used to assess the severity of withdrawal symptoms. For example, the Antidepressant Discontinuation Scale (ADDS) consists of a 30-item checklist that evaluates the intensity of adverse events to discontinuation[12]. Also, the Discontinuation-Emergent Signs and Symptoms (DESS) scale is a 43-item scale primarily used for SSRIs and SNRIs with a temporal ranking of symptom onset in multiple symptomatic domains[7].

As for anticonvulsants, patients that abruptly discontinue benzodiazepines may subsequently experience seizures[2]. Furthermore, patients who suffer from anxiety and suddenly stop benzodiazepines may experience rebound anxiety[5]. Therefore, benzodiazepines should be gradually tapered to mitigate withdrawal effects associated with abrupt discontinuation[5]. Benzodiazepine (Clonazepam, Alprazolam, Lorazepam) withdrawal can manifest as irritability and disturbed sleep and can be managed with flumazenil[16]. Other management strategies include balneotherapy, which is therapeutic bathing, and psychoeducation[17].

Drug withdrawal management is pertinent to patient health. Clonazepam and benzodiazepines can treat SSRI withdrawal in conjunction with SSRI tapering[7]. Furthermore, NMS stemming from medication discontinuation can be managed by diazepam and levodopa/benserazide (Prolopa) after appropriate emergency department interventions as NMS is life-threatening[13]. Also, quetiapine withdrawal can be managed with domperidone throughout tapering[14]. Prolopa and domperidone are not approved or available in the United States. As for treatment options within the United States, a gradual dose reduction of quetiapine, as well as prochlorperazine, may treat discontinuation symptoms[15].

Future initiatives in managing medication discontinuation should prioritize patient-centered care. Patient education is pertinent to encouraging optimal medication adherence and pharmacists are equipped to connect with patients on a personable basis. Ultimately, pharmacists should discuss the possibility of withdrawal effects associated with the discontinuation of certain medication

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Chimeric Antigen Receptor T Cell Therapy (CAR-T) for the Treatment of Relapsed or Refractory Acute Lymphocytic Leukemia

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Acute lymphocytic leukemia (ALL) is the most common childhood cancer in the US, accounting for approximately 25% of cancer diagnoses among children under 15.[i] ALL is a cancer of the bone marrow and blood where the bone marrow makes too many immature lymphocytes (a type of white blood cell). These cancer (leukemia) cells do not work like normal lymphocytes and are unable to fight infection effectively. The increase in the number of leukemia cells in the blood and bone marrow results in less room for healthy white blood cells to fight infection and disease, red blood cells to carry oxygen to tissues of the body, and platelets to form blood clots to stop bleeding. This may lead to infection, anemia, and increase in bleeding. The term "acute" means this type of cancer will progress quickly and may be fatal within months if not treated.[ii] Standard treatment for childhood ALL includes chemotherapy, stem cell transplant, targeted therapy, surgery and radiation.[2,iii]

Almost one in five patients diagnosed with ALL will experience a relapse or refractory leukemia after treatment.[iv] Relapse occurs when patients have a return of ALL cells in the bone marrow and a decrease in normal blood cells after remission. Similarly, refractory leukemia occurs when patients still have ALL cells in their bone marrow after treatment.[v] Five-year survival for patients with relapsed and refractory ALL is less than 10%, demonstrating the urgent need for novel treatment options for these individuals. [vi]

First Approved CAR-T Therapy

On August 30th, 2017, the United States Food and Drug Administration approved Novartis's tisagenlecleucel (Kymriah™), the first chimeric antigen receptor T-cell (CAR-T) therapy. Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.[4,vii] CAR-T therapy is a type of targeted immunotherapy where a patient's T-cells are removed from the patient and then

engineered to attack certain proteins on the surface of cancer cells.[7] After the T-cells are removed from the patient, they are genetically modified to include a chimeric antigen receptor that directs the T-cell to target and kill leukemia cells that have a CD19 antigen on the surface.[4] CD19 is an attractive target because this B-cell surface protein is expressed on nearly all B-cell ALLs.[8] These modified T-cells, called chimeric antigen receptor (CAR) T cells, are grown in a laboratory setting and then infused back into the patient. The CAR-T cells multiply in the patient's body and will recognize and kill cancer cells.[2]

Tisagenlecleucel is a one-time treatment. It has provided a treatment option where limited options exist for refractory or relapsed ALL and has shown improvements in remission and survival rates in clinical trials compared to the current standard of care. The safety and efficacy of tisagenlecleucel were demonstrated in the open-label, multicenter, single-arm Phase II ELIANA trial of 63 pediatric and young adult patients with relapsed or refractory B-cell precursor ALL. In this trial, overall remission rates within 3 months of treatment were 83% (52 of 63; 95% confidence interval [CI]: 71%-91%). In addition, no minimal residual disease, a blood marker that indicates potential relapse, was detected among responding patients. With a median follow-up of 4.8 months from response, the median duration of complete remission was not reached (range 1.2 to 14.1+ months) (95% CI: 7.5-NE). Median time to onset of complete remission was 29 days with onset of complete remission between 26 and 31 days (96% of responders).[7]

Tisagenlecleucel carries a boxed warning for cytokine release syndrome (CRS) and neurological events. CRS is an inflammatory response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms. Because of these life-threatening side effects, tisagenlecleucel is being approved with a risk evaluation and mitigation strategy.[4] The most common side effects (>20%) in the ELIANA trial include CRS, hypogammaglobulinemia, infections (pathogens unspecified), pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury and delirium.[7] Most symptoms appear within one to 22 days following treatment. Novartis is required to conduct a post-marketing observational study to further evaluate long-term safety.[4]

Paying for Tisagenlecleucel

This first in class medicine comes with a one-time treatment price of $475,000. According to cancer experts, it is possible that total therapy costs may reach $1 million or more per patient due to "life-threatening complications that require lengthy hospitalizations and expensive medications".[9] In order to balance patient access to life-saving medicines with economic realities, the Centers for Medicare & Medicaid Services and Novartis are developing an outcomes-based reimbursement

model.[10] In this arrangement, Novartis will only charge for tisagenlecleucel if patients go into remission within one month of treatment.[9] This arrangement will link the reimbursement of the medicine to successful patient health outcomes.

Conclusion

The approval of tisagenlecleucel is an advancement in the treatment of cancer. Based on initial success in clinical trials, CAR-T therapy is being studied for the treatment in other blood cancers, including myeloma and acute myeloid leukemia, as well as various solid tumors.[5] Tremendous strides have been made in the fight against cancer and our knowledge of the disease is only expanding.

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New GLP-1/Basal Insulin Combination Devices for Type 2 Diabetes Mellitus

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The U.S. Food and Drug Administration approved two new injectable combination agents for the treatment of type 2 diabetes mellitus in adults in November 2016. Both of these combination agents include a long-acting basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist. Soliqua® 100/33, manufactured by Sanofi, is a 3-mL multi-dose pen indicated for once-daily dosing with the ability to administer 15 to 60 units of insulin glargine (Lantus®) and 5 to 20 mcg of lixisenatide (Adlyxin®) with each injection.[1] Xultophy® 100/3.6, manufactured by Novo Nordisk, is also a 3-mL multi-dose pen indicated for once-daily dosing, delivering 10 to 50 units of insulin degludec (Tresiba®) and 0.36 to 1.8 mg of liraglutide (Victoza®) with each injection.[2] Please refer to Table 1 for more information about each product.

TABLE 1: COMPARISON OF GLP-1/BASAL INSULIN COMBINATION DEVICES

PRODUCT	**Soliqua®[1]** **(insulin glargine 100 units/mL and lixisenatide 33 mcg/mL)** 	**Xultophy®[2]** **(insulin degludec 100 units/mL and liraglutide 3.6 mg/mL)** 
DOSING	**Initial (on <30 units of basal insulin):** 15 units daily (5 mcg lixisenatide) **Initial (on 30-60 units of basal insulin):** 30 units daily (10 mcg lixisenatide) **Titration**: adjust dose by 2-4 units each week **Daily max**: 60 units insulin glargine/20 mcg of lixisenatide	**Initial:** 16 units daily (0.58 mg liraglutide) **Titration**: adjust dose by 2 units every 3-4 days **Daily max**: 50 units insulin degludec/1.8 mg liraglutide
ADMINISTRATION	No reconstitution needed; inject subcutaneously into the abdomen, thigh, or upper arm	
	Administer one hour before the first meal of the day	Administer with or without meals around the same time each day
STORAGE	Refrigerate unopened pens; store opened pens at room temperature	
	Discard opened pens after 28 days	Discard opened pens after 21 days
A1C LOWERING	~0.5% vs. insulin glargine alone[3]	~1% vs. insulin degludec alone[4,5,6]
WEIGHT LOSS	~1.4 kg vs. insulin glargine[3]	~2.5 kg vs. insulin degludec[4]

When compared to basal insulin alone, Soliqua® and Xultophy® have comparable rates of hypoglycemia as well as greater A1C lowering capability and less weight gain.[3,4] The LixiLan-L trial compared Soliqua® to insulin glargine 100 units/mL.[3] The study included 736 type 2 diabetes patients with a mean baseline A1C of 8.1%. The study population was on average 60 years old and mostly white (91.7%) with eGFR ≥60 mL/min (86.1%) and a mean BMI of 31 kg/m^2. At screening, in addition to insulin therapy, 49% of patients were taking metformin, 40% were taking metformin and another oral agent (sulfonylurea, DPP-4 inhibitor, or glinide), and the remaining patients were taking either a sulfonylurea or a DPP-4 inhibitor or no oral agents. All oral anti-diabetic agents other than metformin were discontinued during the run-in phase. Soliqua® was titrated weekly to a target fasting blood glucose of <100 mg/dL. At the end of the 30-week study, the reduction in A1C from baseline for Soliqua® was about 0.5% greater than that of insulin glargine.

The phase three clinical trials for Xultophy® (DUAL II, III, V) included 1,393 patients with type 2 diabetes who were followed for 26 weeks.[2,4,5,6] DUAL III was conducted in patients converting from liraglutide (baseline A1C of 7.8%),[5] DUAL II in patients converting from insulin degludec (baseline A1C of 8.7%)[4], and the DUAL V in patients converting from insulin glargine (baseline A1C of 8.4%).[6] Across the three studies, the population was on average 58 years old, mostly white (89%) with an eGFR ≥60 mL/min (94%) and a mean BMI of 33 kg/m^2.[4,5,6] In the DUAL III trial, oral anti-diabetic drugs were continued at pre-trial dosing and 74% of patients were on metformin alone, 23% of patients were treated with metformin and a sulfonylurea, either with or without pioglitazone. In the DUAL II and DUAL V trials, patients were treated with metformin in addition to Xultophy® and either insulin degludec or insulin glargine, respectively, and no additional oral anti-diabetic agents were permitted. Xultophy® was titrated twice weekly by increments of 2 units to a fasting glucose of 72 to 90 mg/dL in the liraglutide conversion study (DUAL III) and <90 mg/dL in the basal insulin conversion studies (DUAL II, V).[4,5,6] All three Xultophy® study arms had ~1% greater A1C reduction than their comparators. The greater A1C lowering capability seen with Xultophy®, as compared to Soliqua®, may have been due to titration of the agent to a lower fasting blood glucose target. In addition, of note, liraglutide has evidence of improving cardiovascular outcomes, as demonstrated in the LEADER trial.[7]

However, a major limitation of these agents is reduced dosing flexibility as compared to the individual agents. Xultophy® and Soliqua® are also not recommended for patients requiring greater than 50 or 60 units of basal insulin, respectively.[1,2] Additionally, the dosing for the GLP-1 agonist component cannot be optimized unless the patient is using the maximum dose of insulin per injection. Lastly, these agents require retitration even if a patient was previously on basal insulin and/or a GLP-1 agonist

individually. Although similar to their individual components, the common adverse effects of these long-acting basal insulin and GLP-1 receptor agonist combination agents include hypoglycemia, nausea, diarrhea, infection (nasopharyngitis or upper respiratory infection), and headache.[1,2] Like other GLP-1 agonist agents, these combination products contain warnings about potential thyroid C-cell tumors and acute pancreatitis. Despite the limitations of these agents, either product may be considered for patients on basal insulin but require an additional A1C lowering agent, or to reduce injection burden for patients already on separate GLP-1 agonist and insulin agents.

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Interested in contributing an article for the DC-CCP Summer newsletter or becoming a peer reviewer?

Please contact **dcccpnewsletter@gmail.com**

DC-CCP Upcoming Events

Register for ACCP 2018 Global Conference on Clinical Pharmacy
Seattle, Washington
Registration opened: May 15, 2018
Event dates: Oct 20-23, 2018

dc-ccp
District of Columbia
College of Clinical Pharmacy

About DC-CCP

DC-CCP is a non-profit professional association and an independent chapter of the American College of Clinical Pharmacy dedicated to improvements in pharmacotherapy practice, education, and research in the Washington D.C. Capital Region, including the District of Columbia, State of Maryland, and Commonwealth of Virginia. Membership will be open to any licensed or registered health care professional or health care professional student in the Capital Region. Membership in the American College of Clinical Pharmacy is not required to become a member of our organization.

Purpose and Goals of DC-CCP

(A) To promote the rational use of drugs in society
(B) To advance the principles and practice of clinical pharmacy
(C) To promote the full-time, advanced practice of clinical pharmacy
(D) To provide an advanced level of continuing education programs in the area of clinical pharmacy and objectives of ACCP as outlined in its constitution and bylaws
(E) To provide a forum for the expression of opinion on pharmacy practice, education, and research from the perspective of clinical pharmacists
(F)To support, promote, and advance the goals and objectives of ACCP as outlined in its constitution and bylaws
(G) To provide a local recruiting base for ACCP

For more information or to become a member of DC-CCP please visit our website or social media pages:

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