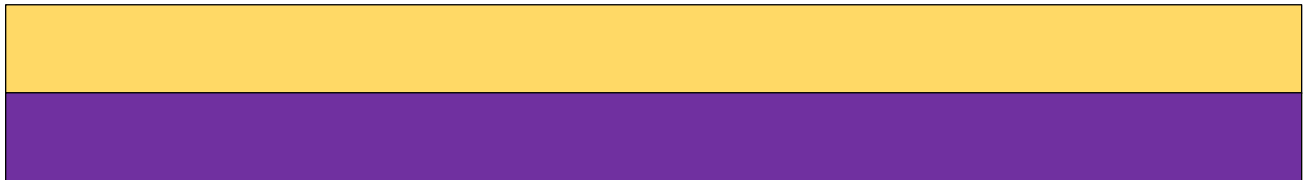


THE OAK LEAF

LSUA'S JOURNAL OF TEACHING AND RESEARCH



Volume 1 Issue 2

THE OAK LEAF: LSUA'S JOURNAL OF UNDERGRADUATE TEACHING AND RESEARCH

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Fall 2021

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CONTENTS

[ESSAY: IMPACT OF WAR ON VETERANS AND THEIR RELATIONSHIPS IN VONNEGUT'S *SLAUGHTERHOUSE FIVE*](#)
 VI NGUYEN WITH MENTOR MATTHEW STOKES..... 4

[BOOK REVIEW: *AMERICAN INDIAN STORIES* WRITTEN BY ZITKALA-SA GARDENIA EVANS AND MARY GUSTIN WITH MENTOR GINGER JONES](#).....12

[BOOK REVIEW: *WE OWN THIS CITY: A TRUE STORY OF CRIME, COPS, AND CORRUPTION*](#)
 RICHARD THOMPSON WITH MENTOR JOHN MARKS.....15

[BOOK REVIEW: *HEALTH AND PHYSICAL EDUCATION FOR ELEMENTARY CLASSROOM TEACHERS*](#)
 MELISSA PARKS.....17

[REPORT: RECENT DEVELOPMENTS IN METAL CATALYZED ALDER-ENE REACTIONS](#)
 EMMA DOWNING WITH MENTOR LAKSHMI VISWANATH.....21

[LITERATURE REVIEW: *STALKING*](#)
 JERAD DANIEL WITH MENTOR JOHN MARKS.....33

[ESSAY: "DRIVING INTO THE HEART OF THE NIGHT": REGENERATE MODERNISM IN THE WORK OF VIRGINIA WOOLF](#)
 OWEN ELMORE.....46

[SHORT ESSAY: THE INFLUENCE OF HISTORY ON THE CHARACTERS IN *NO ONE WRITES TO THE COLONEL*](#)
 TIA MALAK WITH MENTOR GINGER JONES.....53

[REPORT: PHARMACEUTICAL ADVANCES IN COMBATING THE COMMON COLD, HERPES, AND INFLUENZA](#)
 NOAH DEMOSS, GRANT MARTIN, WILLIAM NEWMAN WITH MENTOR LAKSHMI VISWANATH.....56

[CODA](#)
 GINGER JONES.....79

[CONTRIBUTORS](#).....80



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IMPACT OF WAR ON VETERANS AND THEIR RELATIONSHIPS IN VONNEGUT'S *SLAUGHTERHOUSE FIVE*

TABLE OF
CONTENTS ↑

In the novel *Slaughterhouse-Five*, Kurt Vonnegut depicts the intricate ways in which war trauma impacts veterans and their relationships following a war. Vonnegut presents the bombing of Dresden and war trauma using science fiction, an atypical approach when describing a notable and infamous occurrence. He sheds light on how war trauma distinctively affects one Billy Pilgrim's relationship with his loved ones, causing a disconnect from his ability to effectively communicate with them in a way that they will understand. Through the character Billy Pilgrim, Vonnegut reveals the psychological detachment that war victims commonly experience when they return to post-war life.

Billy Pilgrim is not ready for war by any means and has difficulties making it out alive by himself. He frankly does not care for his life at all. He believes, "the marksman should be given a second chance" when shots are being fired at him and his fellow soldiers, and he refuses to duck for cover (Vonnegut 42). Billy would often tell the other members of the "Three Musketeers," "You guys go on without me" when he feels too defeated to move forward (198). Since Billy lacks survival and war instincts, he is continuously pushed around by another "Musketeer" named Roland Weary, who is present for a significant portion of Billy's experience in war. Weary has a misconception of war in that he fails to understand the true meaning of the words "war hero." Because of his selfish and insecure motives for trying to prove a heroic act, Weary knows what it feels like to be left behind. The omniscient narrator explains that Weary "was always being ditched in Pittsburgh by people who did not want him with them" and "It made Weary sick to be ditched" (Vonnegut 44).

Weary's intentions can be perceived in one or two ways: either his insecurity comes into play as an aspect of his character that he does not want anyone else to feel the betrayal of being left behind, or he uses his insecurity to justify his idea of a war hero.

Despite the hostility that he inflicts on Billy, Weary has never left Billy Pilgrim behind to fend for himself. Weary would often curse at Billy, kick him, and slap him in order for him to move. According to Weary, "It was absolutely necessary that cruelty be used because Billy wouldn't do anything to save himself" (Vonnegut 43). In a sense, this could demonstrate Weary's compassion towards Billy, who is so carefree about life and death. Despite Weary's seemingly kind gestures, he blames Billy for his own imminent

death from gangrene that started in his feet (101). Weary made it known that Billy Pilgrim was the cause of his death, and he seeks "to be avenged" (101). Weary's intentions are not out of compassion nor generosity, but out of his deceiving and selfish motives. Weary is humiliated at the simple fact that he went so far to save Billy's life, and now Weary is the one to die. He is so embarrassed that he wants everyone to know that Billy is to blame, completely disregarding the awful circumstances that the soldiers have encountered. Weary never truly war becomes the war hero that he characterizes himself to be. He is more concerned about seeking revenge upon Billy instead of lying down with honor and pride that he has fought for so long. In short, the relationship that Weary and Billy shared was one-sided and benefited Weary's ego that stemmed from his insecurities.

Although the soldiers face treacherous conditions, Billy is certain his life is not going to end due to war but because Paul Lazzaro, another American soldier, vows to kill Billy after the war. Lazzaro believes that Weary "died on account of this silly cocksucker here" and promises to "have this cocksucker shot after the war" (Vonnegut 179). As C. Barry Chabot suggests, Paul Lazzaro cannot be blamed for his "craven and vicious" motives to kill Billy after the war because just like Billy, he is "merely another bug caught in a particular piece of amber" (Chabot 211). Billy is comfortable and accepts that death can occur at any instant because he is aware that he will still be alive at another moment in time. Chabot writes, "the utter passivity of Billy Pilgrim throughout his life comes to seem prescient once he has been schooled on Tralfamadore [a fictional planet]" (Chabot 211). Billy finds comfort and reassurance in the Tralfamadorians' words and lives by them to get through the losses that he has faced. He uses the Tralfamadorian philosophy to justify Lazzaro's motive to kill him, completely unfazed by the fact that Lazzaro will be out to get him once the war is over.

During the war, Billy is a chaplain's assistant, so he does not meet the standard expectations of the other soldiers, who treat Billy with less respect. A prime example of Billy's mistreatment occurs when he is trying to find a place to sleep in the railroad boxcar. When Billy tries to nestle next to another soldier, the man says, "It's you, all right. Get the hell out of here," which causes Billy to be "close to tears" (Vonnegut 99). The constant dismissal leads Billy to "sleep standing up, or not sleep at all" (100). When the American prisoners arrive at the camp, they are ordered to a mass shower where they are cleansed from all the bacteria and lice they have accumulated. The prisoners are issued their coats, and Billy is given "a coat from a dead civilian. So it goes" (104). While the other soldiers are issued with proper coats, Billy is the only one who is issued an ill-fitting coat from a dead man.

Throughout the ride to the prison camp, Billy and a former hobo build a cordial relationship that does not last long. The former hobo continuously tells Billy, "This ain't bad" and "This ain't nothing at all" (Vonnegut 89). The former hobo is the only person who accepts Billy and, in a sense, provides comfort that Billy is not aware he needs during

such a daunting time. On the eighth day in the boxcar, the former hobo says to Billy, "I can be comfortable anywhere" (100). However, "[on] the ninth day, the hobo died. So it goes" (100). By being in the same proximity of his friend's corpse—a friend who had just been alive a few hours ago and claimed, "this ain't bad"—Billy loses hope (100). The unexpected death of the hobo undoubtedly skews Billy's perception of life and death. Marvasti highlights the suddenness that comes with death and the association with terror that comes with premature death and the difficulty that young soldiers face when they are trying to become accustomed to the fact (Marvasti 6). There was not a single rational explanation for the hobo's death, which contributes to the difficulty of Billy comprehending and moving past it. Vonnegut describes the hobo's death by writing, "The hobo could not flow. He could not plop. He wasn't liquid anymore. He was stone. So it goes" (Vonnegut 102). Ultimately, the hobo's passing is one of the war tragedies that makes Billy so numb and accustomed to the concept of death.

Billy Pilgrim shares a distant relationship with his wife Valencia. Despite her undying love for Billy, he feels that "She was one of the symptoms of his disease. He knew he was going crazy when he heard himself proposing marriage to her when he begged her to take the diamond ring and be his companion for life" (Vonnegut 137). Billy believes that one of his war trauma symptoms was not merely asking Valencia to marry him, but "beg[ging]" her to marry him (137). This begging could be caused by the emptiness and the void Billy feels after the war. Billy desperately longs to have a companion, but he views Valencia as "ugly" (137). Despite the false narrative of a lovely marriage, Valencia has a feeling that Billy is full of secrets, which he is, though he would never admit them to her (154). When Valencia asks Billy about his war experiences, he often gives her short responses, such as "Good" and "Sometimes" because he believes the concept of war would be too complex for her to understand (155). Billy says, "It would sound like a dream" when Valencia asks, "Would you talk about the war now, if I wanted you to?" (155). Although Valencia is willing to listen to Billy and support him sharing his thoughts and feelings, he offers little in the one conversation they have about the war and subsequently never speaks of it to her again.

The planet Tralfamadore provides a fantastical escape away from the real world for Billy. While on Tralfamadore, Billy is given a second chance to build more meaningful relationships compared with those in his life on Earth. Playboy model Montana Wildhack is placed in the "planet's" dome with Billy and, "In time Montana came to love and trust Billy Pilgrim. He did not touch her until she made it clear that she wanted him to" (Vonnegut 170). Montana can be perceived as a figment of Billy's imagination and yet another escape from reality. She appears to be an understanding and attractive woman who sways Billy into being open and trusting with her. Montana is aware of Billy's time travel when she asks, "Where did you go this time? It wasn't the war. I can tell that too" (265). Montana has become so intricately connected and understanding of Billy that she can distinguish the moments and places to which he time travels. Finally, Montana embodies Billy's getaway

from the real world in that they become so interconnected, they even have a baby together. Billy is standing in a real-world bookstore on Earth, sees an image of real-world Montana on the cover of a magazine, yet assures himself that in fact, she is “back on Tralfamadore, taking care of the baby” (262).

No one who has been in combat can truly understand the trauma that follows war; consequently, it is not surprising that veterans may seek comfort from anywhere. In Billy’s case, he shares a more intimate relationship with Montana, who lives on a nonexistent planet, rather than with his real wife on planet Earth. The illusion of being able to start over with someone apart from Billy’s own family provides a false sense of a fresh start. More specifically, Billy’s imagined new life on Tralfamadore resembles a form of therapy.

Billy Pilgrim has two children: a daughter Barbara and a son Robert. Barbara has taken on the role of being the responsible caretaker in Billy’s life following the war and an airplane accident where he was the only survivor. Barbara views her father Billy as senile. Barbara consistently asks, “Father . . . what are we going to do with you?” (Vonnegut 37). Barbara’s question reflects a sense of responsibility on her part and the frustration that she shares concerning her father. Billy never gets angry nor feeds off the frustration that Barbara feels towards him (37). Billy’s son Robert is a misbehaved teenager who ultimately becomes a Green Beret and eventually straightens out. He never had a connection with Billy and the feeling is mutual. The narrator states, “Billy liked [Robert], but didn’t know him very well. Billy couldn’t help suspecting that there wasn’t much to know about Robert” (225). One theory is that Robert’s delinquent behavior in his youth stems from the attention he sought from his father, Billy. Even when Robert comes back from Vietnam after hearing about the airplane accident and his mother’s passing, there is not much of a connection and understanding between Robert and Billy despite his experience in the bombing of Dresden. Veas-Gulani writes, “Often those who marry after liberation never even told their wives or children that they were prisoners” (Veas-Gulani 297). Thus, Billy likely feels ashamed and embarrassed of his war story because it does not showcase him as a heroic, brave figure.

When Billy Pilgrim is present in his time as an optometrist, husband, and father, there is still a barricade that disconnects his loved ones from fully understanding him. There is constantly an obstruction between Billy and his daughter, Barbara, as she continually questions his delusions. When Billy does not notice that the furnace in his home is not working, Barbara responds by saying, “If you’re going to act like a child, maybe we’ll just treat you like a child” (Vonnegut 167). Barbara does not understand that her father is traumatized because of the war and that he is constantly reliving that trauma despite the time that has passed. She does not consider that Billy cannot necessarily resume the normal course of his life because the trauma constantly interrupts his day-to-day life as if time has stopped (Bakhitar para 7). The subliminal relationship that Billy shares with his son Robert proves that Billy has been so occupied with his time traveling that he fails to be present in the moment with his son. Billy’s lack of a real loving relationship with Valencia is

clear when he cheats on her at an optometrists' party (Vonnegut 58). Interestingly, the closest Billy comes to intimacy with someone else is on Tralfamadore. Although Montana Wildhack has been brought to Tralfamadore as a "mate" for Billy, he still shares an intimate and understanding relationship with her (168, 170).

O'Sullivan's refers to a definition of the novel as "a work organized so that it introduces characters, about whose fates we are made to care, in unstable relationships which are then further complicated until the complication is finally resolved by the removal of the represented instability" (180). Billy lacks an emotional connection to the relationships he carries in his life as an optometrist, a father to Barbara and Robert, and a husband to Valencia. The instability that Billy faces in his life on planet Earth prevents mutual understanding, which causes disruption and complications. Billy is given a second chance to redeem himself and restore the disconnection that he faces with Valencia through Montana Wildhack. Despite not being present as a parent with Barbara and Robert, Billy Pilgrim is granted another chance to be a better parent with the imagined child he has with Montana. Planet Tralfamadore provides a sense of fate for Billy by presenting him with an opportunity to rebuild.

After Billy is admitted to a mental hospital, Eliot Rosewater, a former infantry captain is assigned the bed next to Billy's (Vonnegut 128). Billy and Rosewater "both found life meaningless" due to what they have seen in war (128). Rosewater took the life of a fourteen-year-old fireman, mistaking him for a German soldier, and Billy witnessed "the greatest massacre in European history" (128). Rosewater is a fan of science fiction and introduces Billy to author "Kilgore Trout [who became] . . . Billy's favorite living author and science fiction became the only sort of tales he could read" (Vonnegut 128). The mental hospital fails to give Billy a proper diagnosis and offer any coping mechanisms (Vees-Gulani 298), which leads Billy to fall into his own unusual form of healing where he does not necessarily move forward but instead, changes his perception of the timeline of his life. If the mental hospital had provided Billy with the proper care and diagnosis that he desperately needed instead of blaming Billy's situation on his father for throwing him into the deep end of the Y.M.C.A swimming pool when he was a little boy, Billy would not have fallen into a false sense of reality (Vonnegut 127).

During his stay in the mental hospital, Billy would often dread his mother's visits because of the unbearable guilt that he felt. Every time Billy's mother came to visit, he would cover his head with his blanket until she left. The narrator explains, "She made him feel embarrassed and ungrateful and weak because she had gone to so much trouble to give him life, and to keep that life going, and Billy didn't really like life at all" (Vonnegut 130). Billy's behavior is an example of how war trauma can impact relationships between loved ones. Billy carries the burden of the treacherous things he has seen in war and in turn, struggles to cope with his trauma after his return to the civilian world. Furthermore, Billy is ashamed of the way he feels and does not know how to express his shame in a way

his mother would understand. Instead, he shuts her out and hides from revealing the truth of his trauma and guilt. Despite Billy's mother's understanding and support for him, he refuses to speak to her about war.

Post-Traumatic Stress Disorder (PTSD) is a mental health condition often triggered by an event in which an individual has a difficult time healing and processing the trauma that he or she has witnessed. PTSD can be seen in many ways, but the four main symptoms that surface soon after the trauma has occurred are: 1) reliving the event, 2) avoiding situations that remind the individual of the event, 3) negative change in beliefs and feelings, and 4) feeling keyed up ("PTSD Basics" para 7-10). The trauma often disrupts daily functions when war veterans return to their everyday lives. One of the most common symptoms of PTSD is reliving the event, where "memories of the traumatic event can come back at any time" ("PTSD Basics" para 7). Veterans affected by PTSD struggle with living normal civilian lives because the traumatic memories can be triggered by the simplest natural occurrence. War veterans who have or are currently experiencing PTSD are more likely to be more on edge, angry, and become overprotective of their loved ones. Often, survivors with PTSD may feel distant from others and feel numb ("Relationships" para 2). War veterans may feel like it is difficult to confide in their loved ones because they are not able to understand and comprehend the trauma the way the veteran does; in turn, this feeling can cause a rift in the relationship ("Relationships" para 4).

War survivors may struggle with harsh anger and aggressiveness. Often, they learn how to suppress these feelings, pushing away and creating a barrier between themselves and their loved ones. They may find temporary stress relief with alcohol or drugs, but these can cause additional problems including addiction. While actively dealing with and processing their traumatic notions, survivors may draw away from their spouses and family in general. According to the U.S. Department of Veterans Affairs, "The survivor's symptoms can make a loved one feel like he or she is living in a war zone or in constant threat of danger" ("Relationships" para 7), which can cause a rift in relationships, and miscommunication that becomes too intricate to dissect. Children can feel like they must fill the role of the parent or behave like them to connect with them ("When a Child's Parent has PTSD" para 5-6). Family members may feel confused and hopeless about what they can do to aid the process of healing or feel that their loved one's healing is their responsibility, which commonly causes depression and frustration.

When it comes to the process of healing from war trauma, the survivor may either seek closeness with their loved ones and be willing to be open to many forms of treatment like support groups or therapy or become distant and sheltered from the outside world and find comfort in substance abuse. The road to recovery ultimately depends on the individual. However, the environment contributes to the individual's healing process as well. According to the U.S. Department of Veterans Affairs, the most beneficial forms of trauma-focused psychotherapies are prolonged exposure, cognitive processing therapy,

and eye movement desensitization and reprocessing (“PTSD Treatment Basics” para 2-4). Antidepressant medications recommended for survivors include sertraline, paroxetine, fluoxetine, and venlafaxine (“PTSD Treatment Basics” para 9). Ultimately, there are different routes to take when it comes to dealing with PTSD, whether it is from a loved one or someone who has experienced it themselves.

Without a doubt, Billy is experiencing a serious form of PTSD that leads him to fall into a fantasy world where he finds comfort in believing that all moments are occurring at the same time. His belief in the planet Tralfamadore causes him to disconnect from his loved ones because they have a difficult time understanding his experiences. When Barbara catches Billy doing something "crazy" such as going on a radio interview and talking about the Tralfamadorians, she immediately calls him out for being senile (Vonnegut 32). Not once has Barbara considered the fact that Billy has witnessed a massacre that has scarred him for life. Despite Billy's constant time traveling to escape his harsh reality, there is one moment where Billy is physically present and can emotionally and mentally feel and understand his traumatic past in the war. As “The Febs” are performing at his anniversary party, Billy “had supposed for years that he had no secrets from himself. Here was proof that he had a great big secret somewhere inside, and he could not imagine what it was” (Vonnegut 221). This event marks a turning point in the novel and Billy's character development because for once, he is not traveling to a different time in life to relive the tragedy (226). For Billy, the performance by the barbershop quartet sparks a realization that there is much to unpack with himself and the trauma he thought was not bothersome.

Billy's detachment from his present world after experiencing trauma is a common coping method for survivors. Billy finds the escape that gives him an illusion that tragedies are not permanent, and deaths are not indefinite. As O'Sullivan mentions, Billy's imagination serves as "an easy escape from the potentially threatening realities of homely wives, reactionary in-laws, aggressive children, and empty lives" (180). Billy is excited about the lessons he has learned from the Tralfamadorians, so he wants to broadcast it to the world so that they could understand that all moments that occur are nonlinear. However, the response that Billy receives repeatedly from his daughter sparks a reminder that outsiders do not understand the Tralfamadorian philosophy. In essence, Billy seeks comfort on Tralfamadore where he is practically granted a second chance with Montana Wildhack and their newborn child. Ultimately, Billy's experience in the war and after the war proves that there is a disconnect and misunderstanding between a war survivor and civilian life.

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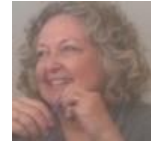


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BOOK REVIEW: *AMERICAN INDIAN STORIES* BY ZITKALA-SA,
EDITED BY MARY MARK OCKERBLOOM (1921)

TABLE OF
CONTENTS ↑

The Dakota Sioux woman Zitkala-Sa (“Red Bird”) or Gertrude Simmons Bonnin, had a traditional Native American childhood before embarking on a journey of education among Whites. Her collection of stories about life on the prairie, *Impressions of an Indian Childhood*, initially published in 1921 and now published online by the University of Pennsylvania, is a thought-provoking historical revelation of the culture of a native people as well as a revelation of the relationship between European Americans and the Native Americans.

The question for most marginalized minorities becomes how to exist in one’s country when it becomes a foreign land. When “paleface” missionaries take Zitkala-Sa from her peaceful childhood home under the guise of civilizing her, Zitkala-Sa comes face-to-face with the choice of whether to assimilate or not.

Zitkala-Sa’s mother nurtured her in an atmosphere of freedom on the reservation of the Dakota Indians where she learned the hierarchy of the family structure in that her older brother became the authority figure in the absence of a father. She also learns the art of hospitality, which is what she sees modeled by her mother. Zitkala-Sa describes her mother’s generosity, even to strangers as a commonplace habit, “At noon, several who chanced to be passing by stopped to rest, and to share our luncheon with us, for they were sure of our hospitality.” Perhaps Zitkala-Sa remembers this time in her life so vividly because her mother often directly involved her in the practice of hospitality. Her mother used to send her to invite their guests, and she recalls, “I was always glad when the sun hung low in the west, for then my mother sent me to invite the neighboring old men and women to eat supper with us.” Hospitality is a keystone of the Dakota culture, and Zitkala-Sa’s mother makes sure to teach her daughter how to be hospitable to both strangers and friends.

When she is about seven years old Zitkala-Sa tries her own hand at hospitality when a tribal grandfather stops by. She recalls, “At once I began to play the part of a generous hostess.” Even though she makes cold coffee with used coffee grounds because she does not know how to make a fire or brew a fresh pot, nevertheless she remembers the significant impact this experience makes on her, “I offered [it] to him with the air of

bestowing generous hospitality.” Zitkala-Sa’s simple act of trying to refresh the body and spirit of a guest in her home demonstrates the incorporation of hospitality into her identity as a young Dakota person.

Zitkala-Sa also learns to be industrious as she understudies with her mother who passes down the fine art form of beadwork. Traditionally, Native American cultures have a rich oral heritage, which captures Zitkala-Sa’s attention as the women gather to recount old legends. This strong parental influence inculcates young Zitkala-Sa with a sense of self. She would need all the strength of character she could muster to survive the separation from her family.

Christian missionaries descend upon the reservation in search of Dakota children to educate, and Zitkala-Sa gets excited about the prospect of living in another land. In her child’s mind, it is not the hope of a quality education that excites her but simply the promise of being able to pick apples from a tree, and a train ride, that lures her away from her childhood home and family who loves her; however, a few red apples from a tree and a chance to ride on a train are pale prizes in comparison to the loss of one’s family and culture for a lifetime.

Because Zitkala-Sa is only eight years old at the time of the missionaries’ invitation, Zitkala-Sa’s mother does not consent immediately to her child’s departure. Zitkala-Sa’s mother sees this hospitable offer as a deception that covers the reality of cultural indoctrination. She knows that the Whites are not being hospitable at all; not so much giving an education as taking their children to make them less Indian and more like White people. Zitkala-Sa recalls her mother’s warning about the missionaries, “Their words are sweet, but, my child, their deeds are bitter. You will cry for me, but they will not even soothe you.” Zitkala-Sa’s mother implies that other needs, either physical or emotional, will go unmet in the White school; however, she acquiesces eventually, with the foresight that “[her child] will need an education when she is grown, for then there will be fewer real Dakotas, and many more palefaces.”

The missionaries, though well-meaning in their religious philanthropic pursuits, are ignorant of the Native American way of life. Zitkala-Sa recalls one singular atrocity committed by the missionaries in cutting off her hair, which they viewed as too heavy, not knowing that Dakotas believed short hair was the mark of a coward. Zitkala-Sa is made to dress in a manner which Dakota women consider immodest and to wear shoes that are noisy and stiff.

When her education is completed, Zitkala-Sa realizes that the “white” education has rendered her uncomfortable in childhood home where her beloved mother “grieved for her.” Zitkala-Sa eventually chooses to make use of the White man’s education to advocate for her culture through her stories. The plight of her race becomes visible as she records it in writing. Zitkala-Sa immortalize her mother’s words and the Dakota habits, establishing

herself as a Dakota woman who has the freedom to choose how much to give and take in life as well as how much to allow others to give to and take from her.

Though her stories do not reveal her personal life, like her mother, Zitkala-Sa married a White man, who supported her fight to honor Native American customs. The New York Historical Society recently created a short, animated film about her life, available on YouTube. And her work is finally being taught in some American Literature courses because the narrative proves to be an enlightening revelation of the intimate, but more importantly, credible cultural lifestyle of a native people. The author masterfully exposes the plight of her people through lucid and delicate vignettes. Zitkala-Sa sheds light on how her culture was Europeanized under the guise of educating of its youth. The reader accompanies Zitkala-Sa on her journey as she struggles with the implications of assimilation. She eventually triumphs as she discovers a means of existing in two worlds. She makes use of her acquired education to immortalize the life of her people through her stories.

We recommend that readers from any cultural background invest attention into this little-known female Native American writer's world. She was once a child with a choice to make—a dichotomy of cultures—and she made room in her identity for both. She weaves the stories of her people like beadwork into our minds, daring us to view a complicated part of American history through the impressions it left on her childhood. Zitkala-Sa's vivid imagery and authentic dialogue combine to leave a deep impression on those who hear her voice as a quiet lamentation for her people and the parts of herself that she ceded to strangers.



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BOOK REVIEW: *WE OWN THIS CITY: A TRUE STORY OF CRIME, COPS, AND CORRUPTION* BY JUSTIN FENTON (2021).

TABLE OF
CONTENTS ↑

Justin Fenton's first book, *We Own This City: A True Story of Crime, Cops, and Corruption*, covers the rise and fall of the Baltimore Police Department's Gun Trace Task Force (GTTF). The author, a crime reporter for the *Baltimore Sun*, was part of the Pulitzer Prize finalist staff recognized for its coverage of the unrest in Baltimore following the 2015 death of Freddie Gray (who was arrested by Baltimore police for possessing a knife—he later died in custody). Anyone interested in criminal justice will find this book helpful in its examination of the siren call of greed's effect on previously honorable police officers. In addition, the book provides a detailed timeline of the rise and fall of the GTTF, a special unit within the Baltimore Police Department which operated in times of high crime with little to no oversight.

Fenton gives a pointed account of the corrupt GTTF, which was an elite plainclothes unit of the Baltimore Police Department. Created to combat the rise in gun crime in the city of Baltimore, the unit was often highly praised by command staff for the number of gun and drug seizures it produced; however, the GTTF was almost completely free of oversight. If the unit boosted stats, police leadership lauded their efforts and fulfilled budget and other requests.

Fenton gives a comprehensive review of the background, career progression, and evolution of the criminal enterprise of the members and the eventual leader of the GTTF Wayne Jenkins. Known and revered throughout the police department as a superstar crime fighter, Jenkins and his team concluded large drug and gun seizures while secretly orchestrating task force officers to conduct robberies, assaults, thefts, as well as falsifying police reports, and being involved in payroll fraud, and drug dealing. Jenkins and his crew were able to disguise their criminal behavior because of Baltimore's rising crime rate, several leadership changes, and the fallout from, and failed prosecution of, the death of Freddie Gray while in police custody. As time passed, Jenkins and his crew became reckless and greedy. Their behavior caught the attention of county and federal investigators and initiated the unraveling of the GTTF.

Fenton obtained news articles, court transcripts, and police personnel files to compile an easy-to-follow timeline for the reader. The well-organized book uses documented sources to tell the story, which is a compelling read as it details the background of corrupt officers and the evolution of their criminal enterprise from honest cops to drug lords and worse. Fenton explains tactics used by most plainclothes and narcotic units, some of which leave complete discretion and freedom to conduct street level investigations. Fenton also intertwines and relates the numerous political and leadership changes which aided the criminal enterprise within the GTTF.

The author includes chapter-by-chapter notes that provide references and/or citations for Fenton's information. Chapter contents illustrate the integrity necessary to serve honorably in a rapidly changing environment with constant access to large amounts of power, drugs, and cash. Professors who teach police ethics courses could utilize this book.

We Own This City brought back memories of my own involvement in undercover narcotics team assignments. The information gives solid perspective of how sometimes a simple push to reduce crime can result in officers who bend the rules, opening the door to absolute corruption. This book takes a hard look at police policies and the result of rampant corruption within an unsupervised police unit such as the GTTF, highlighting failures of the command staff. Fenton's book should be required reading for any criminal justice student, entry level law enforcement officer, or veteran officer pursuing an assignment to an undercover or plainclothes unit.



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PROFESSOR OF EDUCATION

BOOK REVIEW: *HEALTH AND PHYSICAL EDUCATION FOR ELEMENTARY CLASSROOM TEACHERS: AN INTEGRATED APPROACH*, 2ND EDITION, HUMAN KINETICS BY RETTA EVANS, AND SANDRA SIMS (2021)

TABLE OF
CONTENTS ↑

Health and Physical Education for Elementary Classroom Teachers: An Integrated Approach is an inside look at what happens in an elementary health and physical education setting along with the elements needed to guide physical education instruction. The purpose of the softcover book is to promote healthy children in the physical, mental, and social dimensions. This wonderful book addresses both the national health education standards (SHAPE America, 2007) and the national physical education standards which “define what a student should know and be able to do as result of a highly effective physical education program (SHAPE America, 2013). Teachers interested in this genre can benefit from the book by enriching instruction with physical activity at the forefront to promote health across academic subjects.

About the Authors

The authors, Retta Evans and Sandra Sims, embrace quality health and physical education and possess a range of related experiences promoting physically literate and health literate individuals. Evans has a broad background in health education and physical activity and has over twenty years of experience in public schools. She has primarily been interested in implementing strategies to promote health and wellness among youth and has worked collaboratively to develop nutrition policies in schools. Sims has a twenty-year background advocating health and wellness to classroom teachers. Integrating both health and physical education in the classroom is her passion as she continues to create ways to promote active schools, active classrooms, and active bodies.

Contributions

The second edition of the book was launched during the COVID-19 era in spring 2021. This is noteworthy since teachers, despite predicaments like COVID-19 outbreaks, must be ready, willing, able, and flexible to promote active engagement among students at any level with strategies that meet educational, and curricula needs regardless of the unplanned events that can and will occur. When a health crisis happens, practicing hand cleanliness, respiratory hygiene, proper nutrition, and adequate exercise are essential for a strong immunity system. Strategies for promoting a healthy system are incorporated into

Evans' and Sims' second edition. The book will not disappoint as teachers can learn to implement strategies as tools that contribute to health achievement among students for everyday success.

Evans and Sims capture in their book how illness and disease evolved, how advancements in medicine improved quality of life and life expectancy, and how teachers are positioned to enforce positive strategies throughout the school day to promote lifelong health and physical literacy among children. The book introduces the health risk behaviors common among today's youth and health gaps contributing to poor health. The book is an excellent read for classroom teachers wishing to keep abreast of health barriers, negative health practices, growth and development among students while keeping in mind strategies to encourage the importance of good health leading to academic achievement. The book informs teachers of coordinated school health program and the importance of the standards. Health Education is clearly a priority toward the academic and social success of today's students. The National Physical Education Standards are addressed and are linked to quality physical education with a compelling push toward the accumulation of a minimum of 60-minutes of daily physical activity when adhering to the guidelines.

The powerful book references the need for teachers to instill and enforce (or re-enforce) positive health behaviors among children. Even though the first five-years of life establishes health behaviors, the goal is to cause a ripple effect by engaging families. That is, when a teacher introduces skills to promote health, children practice during academic lessons, then go home and practice skills with families in hopes that good practices continue to permit re-enforcement across a spectrum, and so the ripple begins.

Health and Physical Education for Elementary Classroom Teachers: An Integrated Approach includes a wealth of information that belongs on the bookshelves of every aspiring teacher, veteran teachers, and parents. The 227-page book covers health in a nutshell and the impact on school health in a range of topics on health dimensions such as physical, mental, and social. The meat of the book relates to physical activity. Evans and Sims stress the approach of physical activity and academic integration to promote an active school day for all. Classroom teachers are movement educators, and it is pertinent that their students are allowed "out-of-chair-time" to interact with content through physical activity. The key is "moving to learn" once students obtain the tools in the classroom to do so. Incorporating "brain breaks" such as jogging in place between subjects, walking around the classroom, playing Rock, Paper, Scissors, or standing alongside of desks to stretch after taking a test, sitting all morning, or preparing for that long bus ride home after becoming sluggish in a sedentary environment is another approach. What a great idea to move in the classroom, a plot promoted in the book! Children are not designed to endure long hours of sitting. In fact, children already have movement built into their systems; they are born movers and need an outlet during the school day to let it go! Evans and Sims are entrusting teachers to make this happen. Movement in the classroom, no matter the duration,

energizes body and mind. Wondering if students older than elementary can benefit from physical activity integrated into academics and brain breaks? The answer is yes! This is the best kept secret! Evans' and Sims' ideas transition to any level and that is the beauty of their book. "Moving to learn" works for students—elementary, middle school, high school, and university--in being recipients of academically integrated lessons with physical activity and brain breaks. Like elementary students, middle school, high school, and university students need an accumulation of physical activity throughout their day, and they need involvement with academic content by "getting out of their chairs", with the goal to promote student achievement in a healthy, safe, and productive manner. The positive activity behaviors learned from the book must trickle from the elementary school and beyond since early engagement in physical activity is the intervention toward being physically active later in life. (Which is why twelve years of physical education is highly important, but this is another topic on another day!)

Not only is this easy-to-follow, well-structured book a strength, but so is its inclusion of useful components such as quotes, pictures, diagrams/tables/charts within the structure of the chapters that cover multiple topics. Chapters begin with quotes by famous educators or philosophers, an excellent way to begin classroom discussions. The pictures included in each chapter reflect fairness toward gender, race, ethnicity, and ability/disability as represented in society. Even the image on the front cover with the students in the classroom depicts the fairness that is visible beyond the cover. The diagrams, tables, and charts are organized with headers to support understanding of information. Other components placed in the beginning or end of the book include table of contents, index, appendixes, glossary, and references. The table of contents and index allow for easy navigation throughout the book when locating topics in this physical-activity-theme-packed book. The appendixes include the health education standards and physical education standards stated readily throughout the book. The glossary includes an alphabetical list of bold-faced terms conveniently located toward the end. The references are identified by chapter, a unique format. A weakness is that the book is ten chapters long and five chapters too short for a 15-week semester. A remedy worthy of noting is to include model lesson plans across disciplines as an additional chapter. A content warning is that a vital component of a school day—recess—is omitted from the book. An extra chapter inserted could relate recess as an integral part of the school curriculum denoting the different objectives unlike that of physical education. Another warning is the omission of a full discussion on sports and athletics. Physical education and sports and athletics are more different than similar. Sports and athletics deserve a chapter spotlight to differentiate from the foundational years of elementary physical education and the importance of this preparation as a true interest in sports and athletics happens in adolescence. Teachers (and parents) need instruction on the appropriate timeframe, guidelines, and objectives for

introducing sports and athletics to youth who display readiness to participate after encountering wide exposure to a variety of activities during the elementary years.

The book has many takeaways for all teachers, experienced and inexperienced. The intention of Evans and Sims is not to develop a physical education instructor in every teacher, but rather to simply encourage across age groups much needed physical activity, a daily requirement. The book is a recommended good read and belongs on the bookshelf of every classroom teacher. *Health and Physical Education for Elementary Classroom Teachers: An Integrated Approach* is a bible for instruction and guidance for implementing health and physical education across disciplines largely for health promotion. Evans and Sims designed a book that addresses major and significant topics worthy of consuming for advocates of health in the classroom. It is pleasing to know that from the book teachers can discover easy, clever, and fun ways to incorporate physical activity throughout the school day. The best part is the discussion on how students (and teachers) can accumulate 60-minutes up to several hours of physical activity before, during, and after school. Teachers have the health education and physical education standards fingertips away for creating lessons while using the book as a reference. Although the book is not about history, teachers experience an American history lesson while exploring decades of health issues across the land and the accomplishments through medicine and technology that impact today's society.

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OVERVIEW: METAL CATALYZED ALDER-ENE REACTIONS

TABLE OF
CONTENTS ↑

Abstract

The alder-ene reaction, commonly known as the “ene” reaction, is a synthetically versatile reaction yielding useful products which find applications in the field of medicine, pharmaceuticals, cosmetics, and industry, affecting almost every aspect of life. Although the ene reaction is a simple pericyclic reaction that can be successfully conducted in any setting, it has remained unfashionable for many years and is often dominated by the related Diels-Alder reaction. Traditionally, Lewis acids are the commonly used catalysts in promoting the ene reactions, however they often require higher temperatures and longer exposure times. New catalytic approaches, including catalysts containing various transition metals and enzymes are being utilized in the development of both intra- and intermolecular alder-ene reactions significantly extending the scope and applicability of the ene reaction. Metal catalyzed ene reactions also called metallo-ene reactions have gained special attention owing to their ability to tailor the stereochemistry of the products. This article provides an overview of metal catalyzed alder-ene reactions conducted within the past decade.

Keywords:

alder-ene reaction; oxidative cyclization; pericyclic reaction; intramolecular, ynamides.

Introduction

Designing and constructing complex organic molecules that can be used in a wide variety of applications is challenging in many respects. With the discovery of multitudes of reactions leading to formation of new carbon-carbon bonds, synthetic chemists were able to efficiently generate several intricate molecules with potential applications [1]. Among the many C-C bond forming reactions, the alder-ene reaction [2] is particularly important due to its synthetic versatility, evidenced by its varied application toward the synthesis of many biologically relevant substrates, including rapid synthesis of complex molecules and natural products [3-5]. The alder-ene reaction was first discovered by Kurt Alder in 1943 [6] following the discovery of Diels Alder reaction in 1928 [7]. The alder-ene is a pericyclic reaction involving six electrons (Figure 1) involving proton transfer from an alkene containing allylic hydrogen (ene donor) to an enophile (ene acceptor) through the concomitant formation of a bond between them [8].

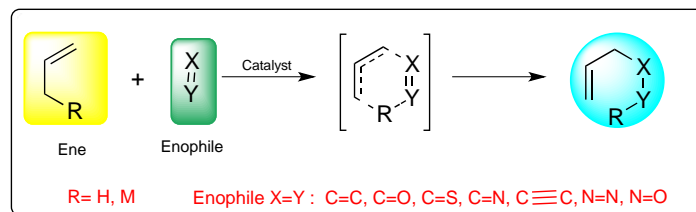


Figure 1. General representation of aldere-ene reaction

The enophile of the reaction must be an unsaturated species with functional groups that include, but are not limited to, an anhydride, aldehyde, ketone, halogen, alcohol, sulfonamide, imide, and ester [9,10]. Considered to be an electronic relative to the diels-alder reaction, the aldere-ene has been relatively less studied despite its significant contributions to the synthetic community. The main reason for this could be attributed to the high activation energy of the aldere-ene reaction which requires the reaction to be conducted at higher temperatures. Hence, exploration of the exact mechanics of the reactions is limited [11]. While it has been elegantly demonstrated that some ene reactions are concerted, there exists many thermal ene reactions which clearly proceed through a stepwise mechanism [8,12].

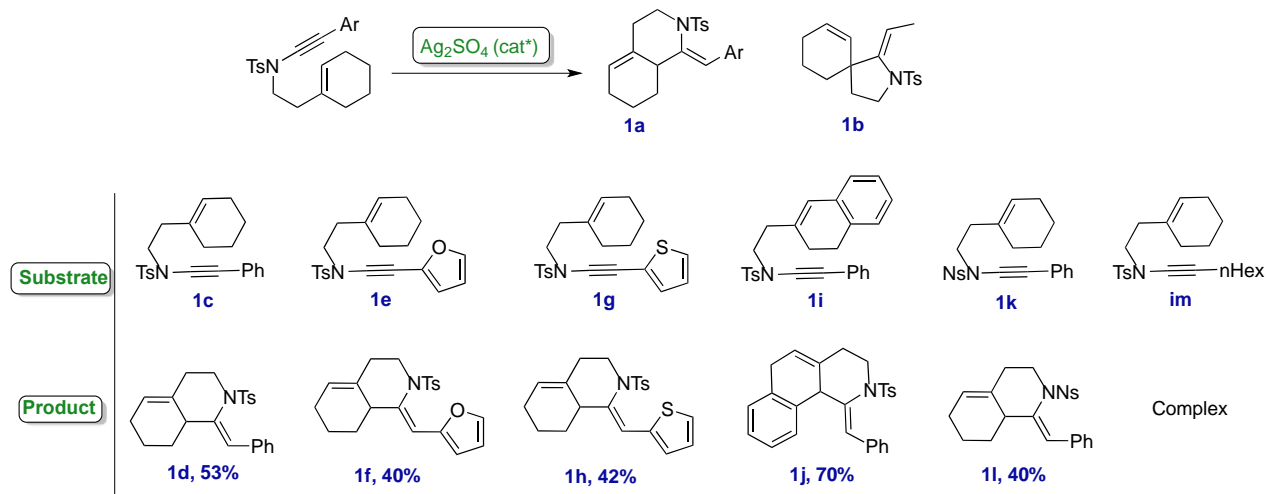
Metal Catalyzed aldere-ene Reactions

One of the main challenges in synthetic chemistry is to uncover and design suitable catalysts to selectively generate products obtained in a complex chemical reaction with high regioselectivity and stereoselectivity. While the complete mechanism of the aldere-ene reaction is yet to be understood, it is believed that high levels of stereospecificity can be achieved through organized transition states. Under typical conditions, the ene reaction must be initiated at extremely high temperatures which is essential for breaking the allylic C-H sigma bond. However, utilizing catalysts can facilitate aldere-ene reactions at milder conditions. A multitude of catalysts have been used to fund this reaction, including Lewis acid catalysts [11], metal-based catalysts [13-14], as well as some by enzymes [15]. With recent developments in metal catalysis, the ene reaction has gained a new renaissance facilitating the reaction to be conducted with relative ease and feasibility. The role of metal catalysts is to accentuate the electron withdrawing effect of the ene acceptor to promote a facile proton transfer to occur in this pericyclic reaction. Over the years many metal catalysts have been utilized in both inter- and intramolecular aldere-ene reactions and the scope of this article is to provide a review of such reactions conducted in the past decade. For each of the metallo-ene reactions specified below a representative reaction has been presented.

1. Silver catalysed aldere-ene Reaction
2. Palladium catalysed aldere-ene Reaction
3. Nickel catalysed aldere-ene Reaction
4. Gold and Copper catalysed aldere-ene reaction
5. Cobalt catalysed aldere-ene reaction
6. Ruthenium catalysed aldere-ene reaction

Silver Catalyzed alder-ene Reaction

In very recent history, Mei-Hua Shen and co-workers discovered an unusual type II alder-ene reaction when electron rich enamines were reacted with metal catalysts [16]. 1,6-Enyamides were first reacted with catalytic amounts of rhodium complex $\text{RhCl}(\text{PPh}_3)_3$ to give the fused bicycle 1a although the spiro 1b was the expected product (Scheme 1).



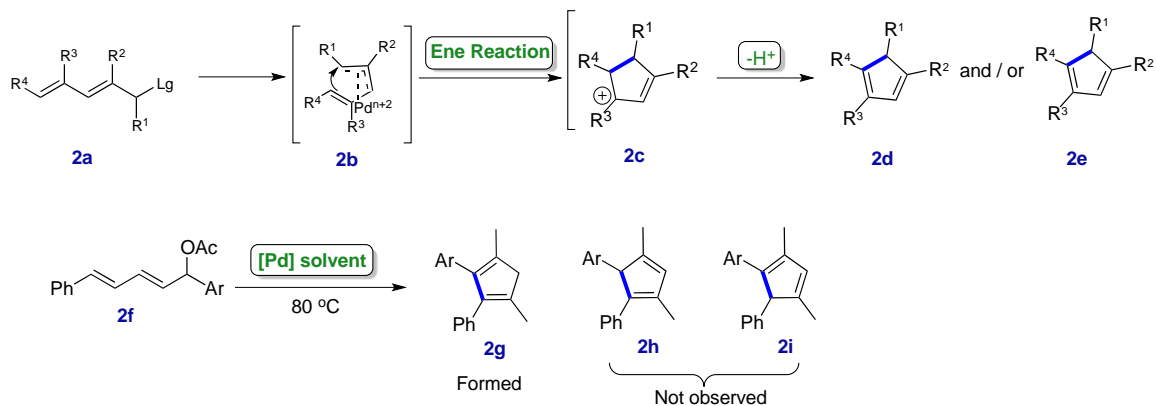
Scheme 1. Type II alder-ene cycloisomerization of N-sulfonyl enamines using silver sulphate

The reaction was then carried out with other metal catalysts (CuCl , CuSO_4 , AgOTf , Ag_2SO_4 and AgSbF_6) using toluene as the solvent. From the experimental results it was concluded that Ag_2SO_4 performed better than the rest of the catalysts used. With Ag_2SO_4 as the catalyst, further studies conducted employing different solvent media (dichloroethane, toluene, dichloromethane) indicated that the most favorable solvent to conduct the cycloisomerization was dichloroethane which produced 55% yield of product at 80 °C. Following the same reaction conditions various N-Ts Ynamides containing phenylethynyl (1c), furanyl (1e) and thiophenol (1g) substituents were subjected to the cycloisomerization procedure to give the corresponding octahydroisoquinoline (1d) and N-heterobicycles (1f, 1h). Benzene fused cyclohexene substituted N-Ts Ynamide (1i) produced a tricyclic product (1j). Trading the N-tosyl for an N-nosyl substituent offered the same results. With alkyl ynamide (1m) a complex reaction mixture was observed which when studied by NMR spectroscopy revealed the occurrence of hydrolysis of both substrate and reactants along with isomerization. This concluded that aryl ynamides were suitable candidates for this type of alder-ene reactions. The proposed mechanism involving a ketene iminium silver intermediate also explains the Z-configuration of the exocyclic alkene and the preferential formation of type II product over spiro type I-ene product.

Palladium Catalyzed alder-ene Reaction

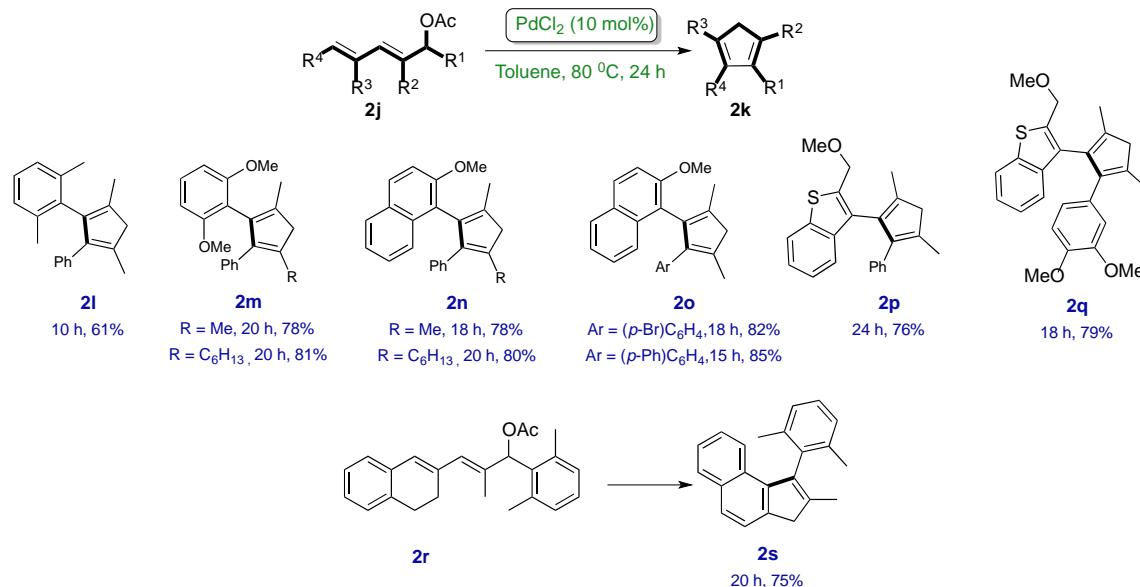
Inspired by Trost and Oppolzer's palladium catalyzed alder-ene reaction [17], Bankar and Singh devised a new route for the synthesis of cyclopentadienes, indenes and cyclopentene fused heteroarenes from 2,4-pentadienyl acetates through a PdII-promoted intermolecular Alder-ene reaction without the use of additives, re-oxidants or bases [18]. An interesting feature of this reaction is that it involved the formation of a new $\text{sp}^2\text{-sp}^2$ C-C

bond. The hypothesis postulated by the team involved an acid-free iso-Nazarov reaction where the dienyl acetate **2a** when reacted with a palladium catalyst generated the vinyl (p-allyl) palladium species **2b** (Scheme 2). Subsequent intramolecular Alder-ene type reaction of the vinyl palladium species yields the cyclopentenyl cation **2c** which then loses a proton to form products either **2d** or **2e**.



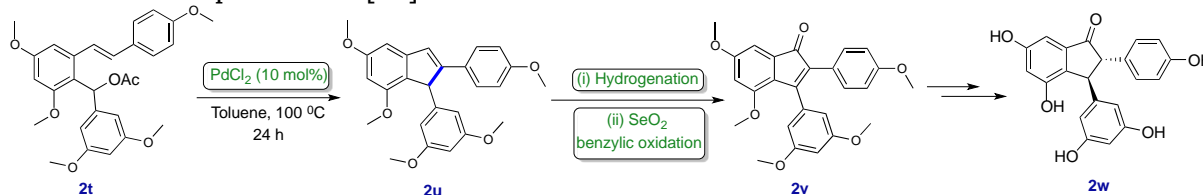
Scheme 2. Palladium catalyzed intramolecular alder-Ene reaction of 2,4-dienyl acetates

Accordingly, substrate **2f** was then chosen to be a model substrate to react in different combinations of metal catalysts and solvents. Pd⁰ catalysts, Pd(PPh₃)₄ and Pd₂(dba)₃ produced no product. With PdCl₂ and Pd(OAc)₂ the tetrasubstituted cyclopentadiene product **2g** was formed, and its structure was rightly distinguished from the other expected products (**2h**, **2i**) by HNMR spectroscopy and single X-ray crystallography. With Ni(cod)₂ and Ir(cod)Cl₂ catalysts no commendable results were obtained. Additional experiments done by altering the reaction parameters including mol% of catalyst used, reaction time and solvents led to the utilization of 10 mol% of PdCl₂ catalyst with toluene for better yields. Using the optimized reaction conditions, several tetrasubstituted cyclopentadienes containing sterically and electronically diverse substituents were synthesized from dienyl acetate **2j** (Scheme 3). Most interestingly the substrate **2r** generated cyclopenta- $[\alpha]$ naphthalene derivative through the alder-ene aromatization sequence.



Scheme 3. Substrate scope of 1,2,3,4-tetrasubstituted cyclopentadienes

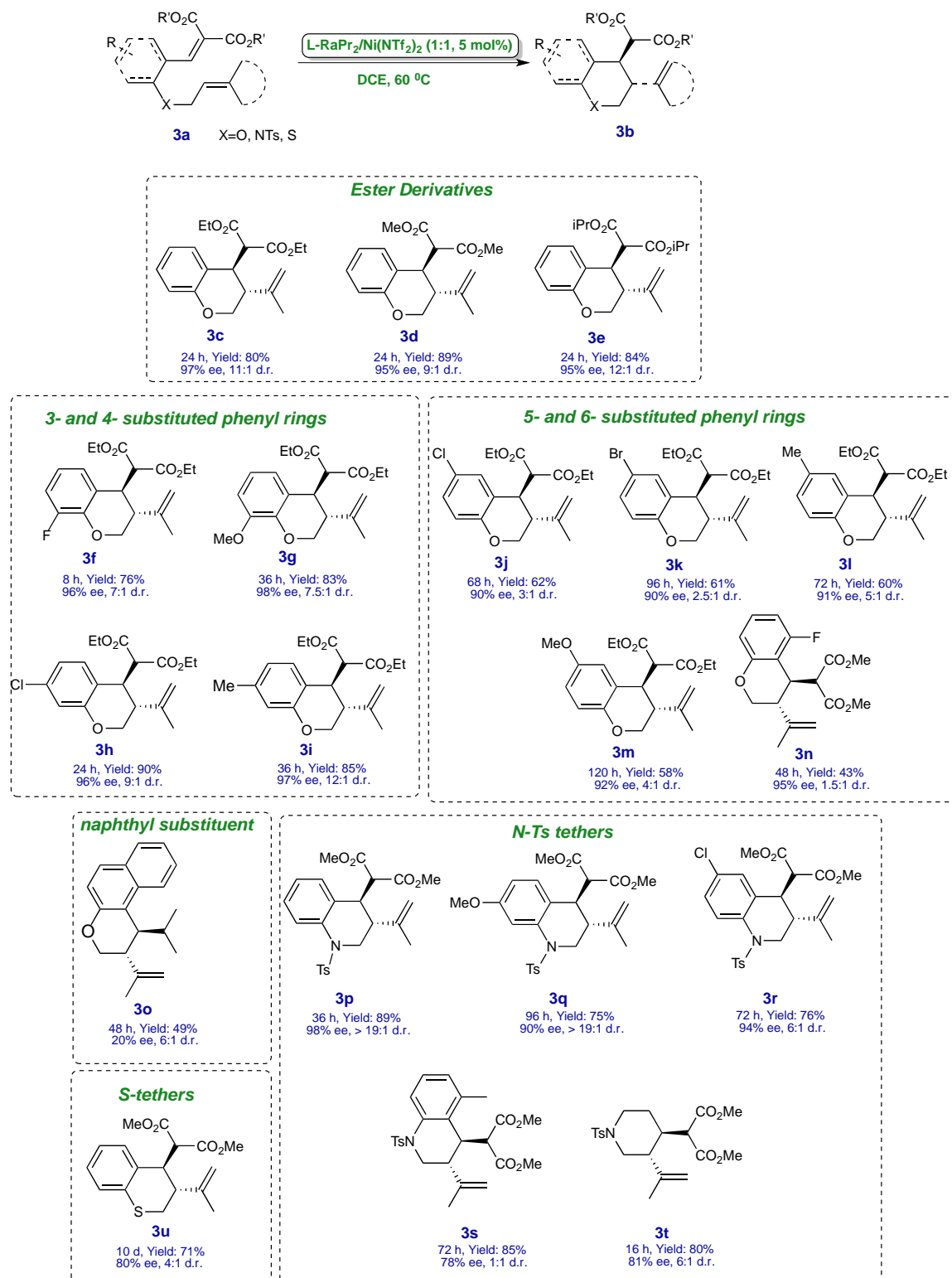
Adopting similar reaction conditions, the group was able to synthesize electronically diverse indenenes and cyclopentene-fused arenes and heteroarenes which find wider applications in material science and in medicinal chemistry. One such application is in the total synthesis of paucifloral, **2w** (Scheme 4), wherein the synthesized acetate **2t** undergoes Pd II promoted cyclization to provide the indene **2u**. Hydrogenation of the indene derivative followed by SeO₂-mediated benzylic oxidation, provided the enone **2v** a valuable intermediate for paucifloral [10]



Scheme 4. Utilization of alder-ene reaction in the synthesis of Paucifloral

Nickel Catalyzed alder-ene Reaction

In 2019, Wen Liu et al., developed a highly diastereo- and enantioselective intramolecular alder-ene reaction of an alkene enophile using chiral N,N'-dioxide/Ni(II) catalyst [19]. Their synthetic protocol offered a convenient way to prepare diverse chroman, tetrahydroquinoline, piperidine and thiochroman derivatives from achiral precursors in good yields with good to excellent diastereo- and enantioselectivities. It also paved a way to synthesize optically active piperidine and thiochroman derivatives. For the intramolecular reaction to occur, 1,7-dienes in which a heteroatom (O, N or S) containing tether was used to connect an α,β -unsaturated ester and an alkene bearing an allylic hydrogen (Scheme 5).



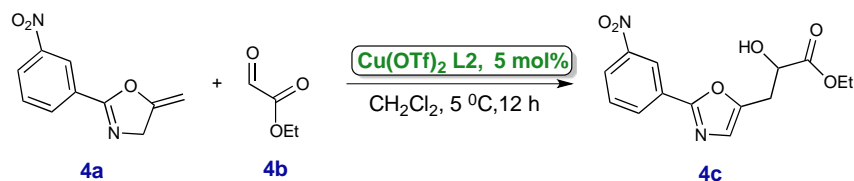
Scheme 5. Nickel catalyzed intramolecular alder-ene reaction

To optimize the reaction conditions, a variety of metal salts/ligands were chosen to react with 1,7-dienes containing the oxygen-incorporated tether in an intramolecular alder-ene reaction. Best results were obtained when L-RaPr₂/Ni(NTf₂)₂ was used as a catalyst.

Decreasing the steric hindrance in the amide moiety of the ligand caused a significant reduction on the enantiomeric excess (ee) values of the products. Investigations on the substrates provided some interesting information. Replacing the ethyl ester moiety of alkylidene malonates with a methyl (3d) or an isopropyl group (3e) gradually increased the diastereoselectivity. The position of substituents on the phenyl ring was also found to cause significant changes in the outcome of the reaction. Phenyl groups with substituents at 3- or 4-position yielded products with high yield and selectivity (3f-3i). Electron-withdrawing substituents present, especially at the 5- or 6-position of the phenyl ring, decreased both the yields and the diastereomeric ratio dramatically with their enantioselectivity preserved (3j-3n). Switching the phenyl to a naphthyl group also decreased considerably the yield and the ee value (3o). While the enantioselectivity of the tetrahydroquinolines obtained using N-containing tethers remained unaffected, the position of the substituents played a major role in determining the diastereoselectivity of the products obtained (3p-3t). For the synthesis of thiochroman derivative (3u), where sulfur is present in the linking unit, a longer reaction time and high temperatures were recorded.

Gold and Copper Catalyzed alder-ene Reaction

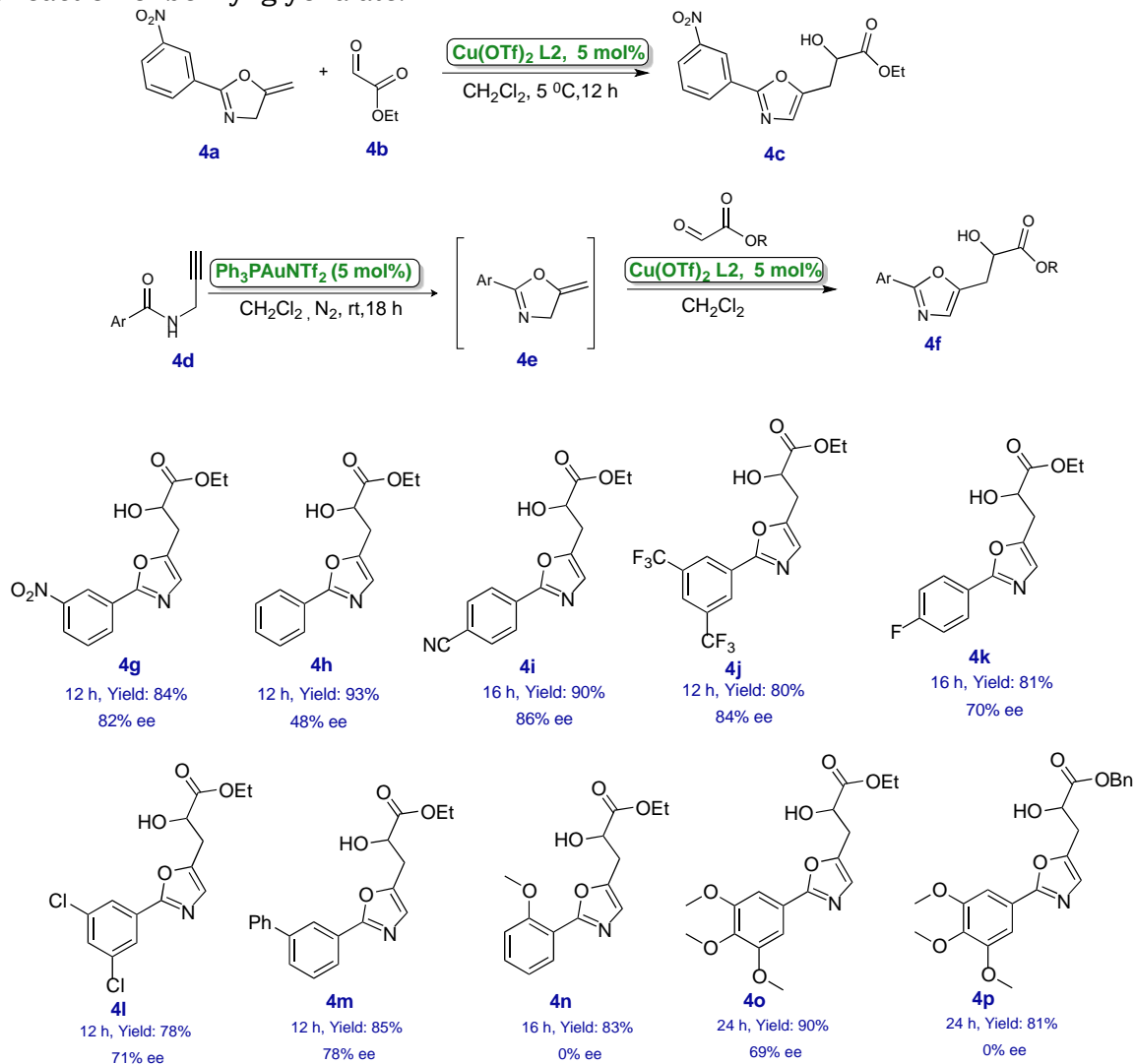
A highly efficient one pot sequential reaction protocol for the enantioselective synthesis of oxazole alpha-hydroxy esters using copper and gold catalysts was developed by Nalivela and Hashmi [20]. A series of experiments were conducted utilizing different metal catalysts and a chiral ligand combination to perform the alder-ene reaction between alkylideneoxazoline, 4a and ethyl glyoxal, 4b (Scheme 6). Initial experiments with (i-PrO)₂TiCl₂, in combination with chiral ligand (S)-(-)-1,1'-bi(2-naphthol), offered products in good yields but with poor enantioselectivity. Efforts were made to increase the enantioselectivity by changing the catalysts, ligand and other reaction parameters such as time and temperature.



Scheme 6. Copper catalyzed alder-ene Reaction

Employing Cu(OTf)₂ with 5 mol % of the ligand (S,S)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline) in CH₂Cl₂ at -5 °C for 12 h resulted in optimal yield of 86% with 81% ee as determined by chiral HPLC. A gold catalyzed cycloisomerization of 3-nitro-N-(prop-2-yn-1-yl) benzamide was performed to give the corresponding alkylideneoxazoline which was then subjected to the alder-ene reaction using optimal reaction conditions. Despite the presence of a gold catalyst in the one pot mixture, this sequential synthesis was found to be highly efficient with good enantioselectivity (82%) yielding 84% of the desired alpha-hydroxy ester, 4g (Scheme 7). Additional experiments done to explore the substrate scope revealed interesting details. A phenyl ring with no substituents proceeded in the expected manner with high yields but only with moderate enantioselectivity (4h). The presence of electron withdrawing groups (CN, CF₃, halogens) on the meta or para position offered products with excellent enantioselectivity (86%, 84%) and good overall percent yields (4i-

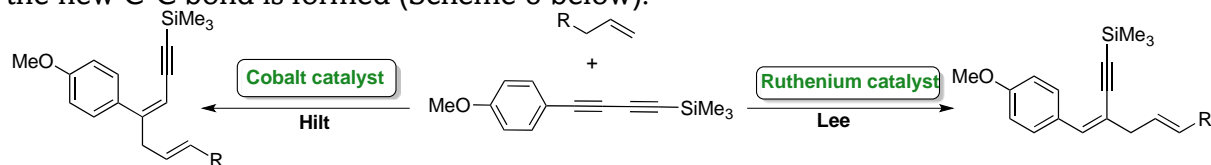
4l). Adding a methoxy substituent in the ortho position (4n) resulted in complete loss of optical excess due to the coordination of the additional oxygen atom. However, groups in the meta- or para positions were well tolerated resulting in good outcomes (4o). The increased steric hindrance of benzyl group yielded only a racemic product (4p) in the alder-ene reaction of benzyl glyoxalate.



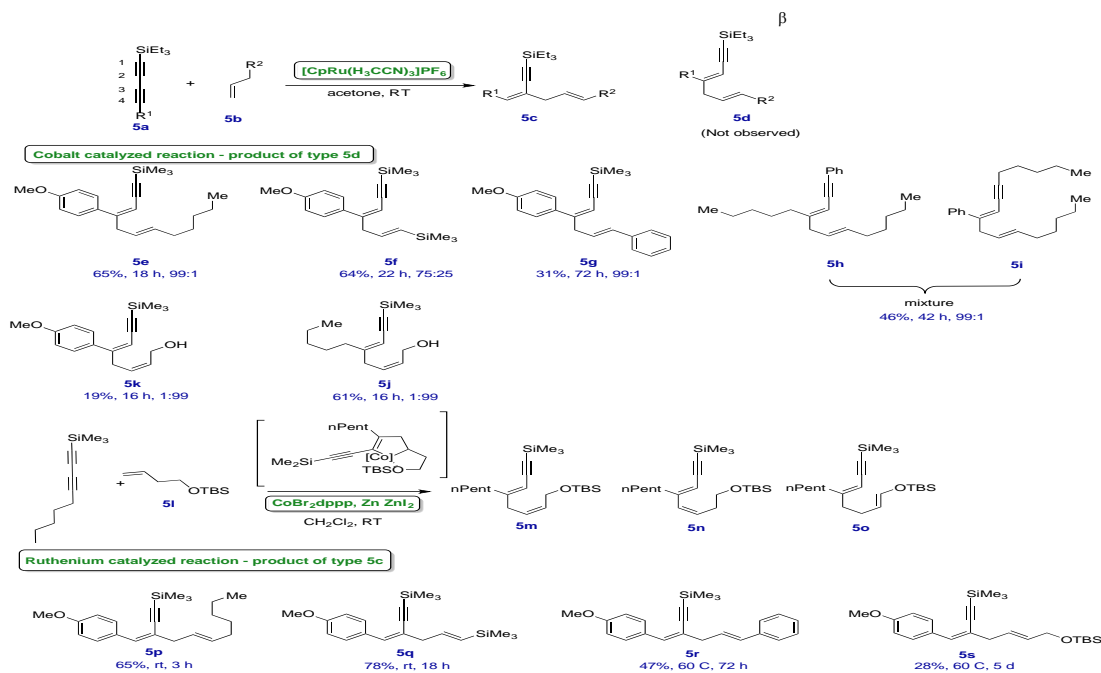
Scheme 7. Synthesis of substituted oxazole alpha-hydroxy esters

Cobalt Catalyzed alder-ene Reaction

Weber and Hilt applied cobalt and ruthenium catalysts to control the regioselectivity in the alder-ene reaction of trialkylsilyl-substituted 1,3-butadiynes with terminal alkenes [21]. The results were complementary generating two different yn-dienes varying at the site where the new C-C bond is formed (Scheme 8 below).



An exclusive chemo selective alder-ene reaction was realized when 1,3-butadiynes containing a trialkyl silyl group were subjected to a cobalt-based catalyst with terminal alkenes. The cobalt-based catalyst is a mixture comprised of $\text{CoBr}_2\text{dpppp}$, Zinc powder and ZnI_2 with terminal alkenes (Scheme 9).

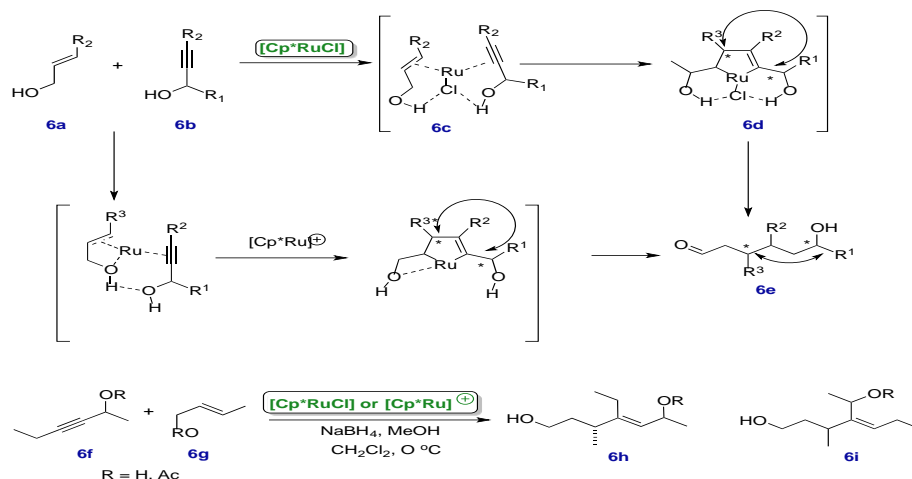


Scheme 9 Cobalt and Ruthenium catalyzed alder-Ene reaction of 1,3-butadiynes with terminal alkenes

The trialkyl silyl group played a leading role in deciding the stereochemistry of the product by way of directing the cobalt catalyst toward the other triple bond forming products of type **5d**. Without the trialkylsilyl substituent both regioisomers (**5h** and **5i**) were obtained with the new carbon-carbon bond forming mainly at the less hindered carbon C1 or C4 of the 1,3 diyne. It was reasoned that the stereochemistry of the alpha double bond was controlled by the formation of a metallocycle. The β -double bond generated by β -hydride elimination of the formed metallocycle is most sterically controlled and produces the preferred E-configured double bond. It is to be noted that when 3-buten-1-ol was used as a terminal alkene, there occurred an inversion in the geometry of the β -double bond due to the coordination of the oxygen atom with the cobalt catalyst (**5k** and **5j**). Attempts to reduce the oxygen coordination leading to an E-configured product by using TBS-protected alcohol resulted in a mixture of products (Scheme 9). With the Ru catalyst, only the branched product of type **5c** was obtained. Most importantly 1,3-diynes demanded a longer reaction time, and with aryl substituted alkenes, a higher reaction temperature was required for the reaction to go to completion. When 3-buten-1-ol was used, the reaction did not proceed to completion even with increased catalyst loading and a high temperature of 60 C whereas in the case of TBS protected alcohol, a single isomeric product **5s** was isolated in 28% yield after 5 days.

Ruthenium Catalyzed alder-ene Reaction

In 2017, Furstner and coworkers used chiral Ruthenium catalysts to conduct a highly regioselective intermolecular alder-ene type reactions of alkynes with 1,2-disubstituted alkenes [22]. The utilization of a neutral or cationic $[\text{Cp}^*\text{Ru}]$ catalyst effectively preorganized a generic pair of unsaturated alcohols **6a** and **6b** in a head-to-head orientation (Scheme 10).



Scheme 10. intermolecular alder-ene reaction with chiral ruthenium catalysts

Oxidative cyclization with subsequent elimination of β -hydrogen leads to the formation of enol **6c** which then tautomerizes to give the corresponding aldehyde **6e**. Reacting a secondary propargyl alcohol, **6a**, and crotyl alcohol, **6b**, in the presence of either $[\text{Cp}^*\text{RuCl}]_4$ or $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ in CH_2Cl_2 followed by reductive work up, produced the 1,4-anti-configured product, **6h** as the major isomer in both cases. The neutral chiral complex $[\text{Cp}^*\text{Ru}]$ offered better stereoselective outcomes with d.r 12:1 compared to its cationic sibling 6:1. With O-Acylated propargylic substrates, no products were realized with either of the catalysts.

Conclusion

The incorporation of transition metal catalysed protocols has led to a new revitalization of the alder-ene reaction, allowing it to be performed under mild conditions with high functional group compatibility and high stereoselectivity. The synthetic applications of the ene reaction are boundless, increasingly peaking the interests of scientists and researchers in the exploration of such reactions. Despite the tremendous efforts that has been put towards the metal catalysed reactions in the past decade, the ene reactions are still in infancy. There are still major challenges that needs to be addressed, including the implementation of reactions with low catalyst loading and solvents that promote green chemistry.

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STALKING: A LITERATURE REVIEW LINKS BETWEEN INTIMATE PARTNER VIOLENCE, STALKING, AND HOMICIDE

TABLE OF
CONTENTS ↑

The use of the word stalking began as an issue involving celebrities who were stalked by strangers, but current research points to an even bigger issue (Melton, 2000). Stalking was initially dramatized by the media to label unwanted actions toward celebrities and other high-profile figures like elected officials (Buhi et al., 2009; Coleman, 1997; Melton, 2000). As Melton (2000) notes, the media initially referred to stalking as simply an annoying and uncomfortable experience but stalking eventually became redefined as violent and dangerous. But as Nobles et al. (2018) says, the culture of our public lives played out over the Internet and in social media has increased the perception that stalking is just a part of life. With social science research, however, stalking is recognized as an occurrence impacting the criminal justice field, a victim's mental health, and the general public's health.

In the early 2000s, stalking as a social issue was in its infancy (Melton, 2000). Stalking victimization was not well-researched (Buhi et al., 2009; Fisher et al., 2002). Decades later, there is still not an overwhelming amount of research. Mullen et al. (1999) note the newness of the term stalking but insist the idea has been around even in fictional stories for over a century.

The research is clear; women outnumber men as the target of stalkers. Fisher et al. (2002) make specific reference to the missing research attention of the stalking of women, noting particularly the limited knowledge of the scope, nature, and risk factors associated with stalking. Furthermore, Burgess et al. (1997) indicated a connection between stalking and domestic violence.

The connection between stalking and domestic violence deserves a closer look. Very recently has there been additional research into the major risk factors specifically relative to intimate partner homicide. Rai et al. (2020) alert us that over 20% of homicides in the United States are committed by an intimate partner. Researchers specifically focus on the connection between homicide victims who are linked to their stalker killers by an intimate partner (current or former) relationship.

This literature review will look at what literature exists that shows the connection of intimate partner violence with intimate partner stalking and how both of those types of

victimizations intersect with intimate partner homicides. The exploration of the literature will begin by defining and understanding what stalking is, reviewing the reporting of stalking, and looking at the effects stalking has on victims. Next, attention will be focused on the relationship of the stalker with the victim and the connection of intimate partner stalkers with intimate partner violence as well as possible links between intimate partner stalkers and intimate partner homicide. Finally, a look will be taken at the criminal justice response to stalking.

What Is Stalking?

Beginning with California in 1990, all 50 states and the District of Columbia now have passed laws addressing stalking (Buhi et al., 2009; Fisher et al., 2002; Melton, 2000). But in a review of the literature, just as the legal definitions in each state may differ depending on the jurisdiction, not all researchers define stalking the same way. Meloy and Gothard (1995) defined stalking as the threatening of someone's security by repetitious following and harassment in a deliberate and malevolent way. Douglas and Dutton (2001) add to that definition by including the actions of a stalker must be threatening in nature and must cause a victim to fear for their safety. White et al. (2020) explain that to understand the definition of stalking, the actions of the perpetrator must be defined, but the reaction by the victim must also be considered in the definition. There is a relationship to when the fear of the victim changes in response to the actions of the perpetrator. A perpetrator's actions can go from being perceived by a victim as appropriate to distressing and causing fear in the victim and ultimately becoming criminal in nature. Over time, it appears the definition of stalking has evolved to incorporate how the behaviors displayed by the stalker specifically affect victims.

Also common among the definitions is that stalkers' behaviors are repetitive. In a survey of stalking victims by Blaauw et al. (2002), respondents indicated stalking behaviors included repeated telephone calls (especially nighttime phone calls), surveillance, unwanted approaches, physical assaults, unlawful entry into their homes, damage to property, theft of property, and threats or harassing letters. Meloy (1996) also reported common stalking behaviors that included phone calls, visiting workplaces or residences, letter writing, following, face-to-face confrontations, and giving unwanted gifts.

Stalking behaviors have also evolved over time especially with advancements in technology. According to Augustyn et al. (2020), stalking can also include unwanted surveillance and tracking by using technology, emails, text messages, and instant messages. Reyns et al. (2011) specifically reference the term cyberstalking, noting this type of stalking includes repetitious harassment, sexual advancement, and threats of violence in an online environment.

Stalkers have proven they can also adapt to stalking within the guidelines of a global pandemic. In a British study of the effects of stalking victimizations during COVID-19 lockdowns, Bracewell et al. (2020) found one stalker employed a private detective to watch

the home of a victim who was on lockdown because the stalker was also on lockdown. There was another stalker who used multiple third-party sources, like family, neighbors, and friends, to keep tabs on a victim. Logan (2019) notes this type of stalking, called proxy stalking, is a particular safety concern to stalking victims, and nearly one-third of stalking victims report experiencing proxy stalking. Bracewell et al. (2020) also noted an increase in the frequency of online stalking behaviors experienced by victims such as revenge porn, stalking by way of creating spoof Facebook accounts of victims, and by contacting victims via Zoom.

Reporting by Victims

Victims of intimate partner violence and stalking make either formal or informal reports (Demers et al., 2018; Reyns & Englebrecht, 2014). Formal reports refer to a victim's disclosure to formal sources like law enforcement, and informal reports refer to a victim's disclosure made to a trusted source like a close friend or family member. Informal reporting by stalking victims is the most common type of disclosure. This is important to note as this affects research that focuses solely on victimizations reported to only formal sources like the police (Nobles et al., 2018). Formal reporting of stalking victimization appears to be lacking. Fisher et al. (2002) conducted a survey that showed stalking victims typically do not use the criminal justice system relative to stalking. In that survey, only 2% of stalking victims indicated they filed criminal charges with less than 4% indicating they attempted to get a restraining order. Augustyn et al. (2020) found only a mere 6% of victims of intimate partner stalking made a formal report to the police.

Specifically, regarding intimate partner violence, Demers et al. (2018) noted researchers found most intimate partner violence victims do disclose their victimization to an informal source. They further indicate there are very few formal reports of intimate partner violence to police with most formal reports occurring especially when there is extreme, repeated violence specifically with young victims and especially when the victim actually fears for their safety. Also noted was that disclosure occurred more often when either the victim or the perpetrator used alcohol.

Like reporting of intimate partner violence, Demers and colleagues further suggested stalking is also underreported, but, like intimate partner violence, it is also mostly disclosed by victims to informal sources. Buhi et al. (2009) reported at least 48% of victims do not report their stalking incident to anybody. As with intimate partner violence, Demers et al. (2018) suggests a catalyst for formal reporting of stalking victimization is when the victim believes they are in danger. Women were also found more likely than men to make a formal report of stalking. In the study, they found 72% of stalking victims disclosed to an informal source but only 8% disclosed to a formal source. With stalking, their research showed a 50% increase in reporting when the stalker was a current or former intimate partner, and females were twice as likely to disclose. Significant in this study is the researchers broke down the disclosure data into disclosure in cases where the stalker was a

current intimate partner and cases where the stalker was a former intimate partner. They found more disclosures occurred when the stalker was a former intimate partner.

In discussing disclosure, it is important to understand a victim's reasons for not disclosing. In a study in Hong Kong by Chan and Sheridan (2020), the first stalking study outside of Western countries, they found that stalking victims preferred to handle the stalking problem themselves, similar to the research results conducted in Western countries. Men, more than women, were found to be more likely to confront their stalkers head-on and issue a warning shot of sorts toward their stalkers. Demers et al. (2018) notes the two most cited reasons in their study for victims not disclosing intimate partner violence and stalking were that their victimization was not severe or serious enough or the victim considered stalking a private issue.

Reyns and Englebrecht (2014) discuss the decisions victims face post stalking victimization. Decisions include the choice to disclose to a trusted confidant and the choice to make a formal police report. They specifically note the lack of formal reporting can directly impact measuring true victimization rates, catching offenders, and providing victims with the support and services they need. In their research to specifically find out what influenced a stalking victim's decision to disclose informally, they found that the more serious a stalking event was, the more likely a victim was to make a disclosure both informally and formally. Fear and feeling the direct effects of stalking in the work environment were both driving forces behind a victim making a disclosure, and the seriousness of the event increased formal reporting more than 20 times.

Impact of Stalking

As noted by Logan (2020), there are millions of both men and women who suffer from stalking victimization yearly. The literature notes victims of stalking suffer a myriad of issues both mentally and physically because of their victimization. In the survey by Blaauw et al. (2002), almost 75% of victims had indicators of a psychiatric disorder. A possible explanation was that stalking victims are often subjected to stress that is inescapable, sustained, insistent, and severe. The more stressful the environment, the more likely a victim was at risk for being in psychological distress. Female victims of stalking especially express a high degree of fear because of stalking as compared to male victims (Logan, 2019). Nobles et al. (2018) indicate victims may suffer post-traumatic stress disorder re-experiencing and even have suicidal thoughts. In their research, they remarked that formal disclosure to both legal sources and healthcare sources was lacking suggesting victims are not receiving appropriate mental health care because of their failure to disclose formally.

Augustyn et al. (2020) note intimate partner stalking victims especially suffer negative consequences of stalking. In the study, over half of the women surveyed reported stalking caused interference with their lives and prevented them from participating in activities. Nearly three-quarters of respondents reported being in an intimidating atmosphere following stalking. Buhi et al. (2009) report female victims of stalking could

suffer depression, anxiety, and posttraumatic stress disorder. Further concerning to Buhi and colleagues is these victims might be at greater risk of being assaulted or suffer forced sexual contact.

The duration of the stalking is important to further understand how stalking affects victims. Victims have reported various durations of stalking victimization. Blaauw et al. (2002) reported victims experienced varying durations of stalking behaviors anywhere from 2 years to 10 years. Some behaviors were reported occurring every day, and some behaviors were reported after a month's long lull. In their study, almost half of the victims reported long-term stalking that lasted for several years. In the research by Fisher et al. (2002), college women surveyed reported stalking occurred for as short as one day in duration to as many as 10 years. They commented that a stalking experience for a college woman is typically not brief and may go on for at least two months.

Chan and Sheridan (2020) noted the global issue of stalking victimization in their study and the effects on the personal health of those victimized by stalking and harassment can be detrimental. They identified the negative effects suffered by Asian victims. Their study suggested the negative effects suffered by victims could be directly related to how the victim copes with their stalking victimization. The research suggests stalking victims have one or a combination of the following coping responses: avoidant, proactive, passive, compliance, and aggressive. In their survey of self-identified stalking victims, researchers found stalking victims were most likely to use passive and avoidant strategies. Males, however, were specifically found to be more likely to use compliance and aggressive strategies adding that males, by social role, may be more willing to confront and communicate directly with their stalker.

Davis and Frieze (2000) explain the differences in the expressed distress between male and female victims of stalking. In their research on stalking victims, they found over 25% of victims did seek mental health counseling. They also indicated stalking victimization caused some victims to arm themselves with a firearm or physically move to another city to try to prevent stalking.

Stalker-Victim Relationship

Douglas and Dutton (2001) estimate about 5% of the US population experiences stalking. According to Melton (2000), the idea that stalking was a more prevalent issue and a shift away from believing stalking is simply a celebrity nuisance toward stalking being a universal problem for women began in the early 1990s. Indicating stalkers are not just strangers, Fisher et al. (2002) found four out of five women knew their stalker. The known stalkers were indicated to be a boyfriend, ex-boyfriend, classmate, friend, acquaintance, or co-worker.

Fisher et al. (2002) notes that college women especially are common victims of stalking stating stalking is in fact the most common type of victimization of college women. Researchers recognized college students commonly are together at similar times in similar

places both on and off-campus with little supervision from adults. Additionally, housing environments with mixed male and female residents, late night-hours of social interaction, drug and alcohol consumption, and a lack of supervision all contribute to exposing college women to an increased risk of stalking victimization.

Davis and Frieze (2000) suggest stalking may be a type of domestic violence that happens mostly when in failed relationships, and most often, those who were in some sort of intimate relationship are later likely to identify as being stalked versus those not in an intimate relationship. The most common victim of stalking is a current or former spouse or intimate partner (Burgess et al., 1997; Coleman, 1997). Augustyn et al. (2020) identified research that found more than 40% of victims of stalking had a current or former intimate relationship with their stalker. Douglas and Dutton (2001) give a higher estimate of 50% to 60% of stalking victims who were once intimate partners. They also note the most common victim of stalking is a former intimate partner and suggest there is a potential link between intimate partner violence and intimate partner stalking.

Augustyn et al. (2020) noted women were most often the victims of intimate partner stalking. This research also noted victims of intimate partner stalking were mostly white females who did not live on college campuses. Buhi et al. (2009) suggests non-students experience more stalking-related violence compared to same-aged college women. Logan (2019) found ex-intimate partner stalkers were more likely to assault and threaten their victims than non-intimate partner stalkers. Also indicated in the research was ex-intimate partners had more unwanted contacts and utilized multiple stalking methods as compared to non-intimate partner stalkers. White et al. (2020) also note many stalkers are ex-intimate partners and look at whether there is a connection between intimate partner violence during the relationship and stalking after the relationship is over. Further explained is that we understand much more today about intimate partner violence, but the same is not true for stalking.

In a British study, Sheridan and Davies (2001) looked at the possibility of certain subgroups of stalkers and compared violent acts from each subgroup. Their subgroups were ex-intimates, acquaintances, and strangers. Violent acts within these groups included both acts against the primary target of the stalker as well as violence toward another party like a victim's friend or family member. They found 49% of their victims were stalked by an ex-intimate partner.

Intimate Partner Violence and Intimate Partner Stalking

As mentioned by White et al. (2020), there is a need to understand the relationship between intimate partner violence and stalking because victims of abuse during a relationship are at even greater risk of becoming stalking victims of their abusers after the relationship ends. Meloy (1996) found any time a verbal threat is made by a stalker, the threat of violence increases, and even if the threat is not actually acted upon more than half

of stalkers make overt threats to their victims. He noted stalking behavior is only occasionally prosecuted criminally despite being a crime in all 50 states.

Logan (2020) explains that with both male and female victims of stalking, threats, and violence before stalking behaviors began was indicative of assault after stalking began. Sheridan and Davies (2001) add ex-intimate partner stalkers were suggested as the most persistent stalkers in the group they studied, and there was a correlation found between an ex-intimate partner stalker threatening violence and an ex-intimate partner stalker actually carrying out that threat. Their research discovered ex-intimate stalkers assaulted their victims in 45% of the studied cases.

When stalking occurs during an intimate relationship or with a former intimate relationship partner, it is a warning that danger may be imminent (Cattaneo et al., 2011). Also suggested by Cattaneo and associates is that, though stalking is believed to be quite prevalent, current, or former, intimate partners are the most likely victims of stalking and have a higher risk of physical and psychological abuse. Davis and Frieze (2000) note the need for more research about stalking as a form of domestic violence. Also noted was the need for more research of a theory that stalking might be more likely to happen in intimate partner relationships that ended unsuccessfully or in a circumstance where a stalker wanted to have an intimate relationship with a particular victim, but the victim did not respond favorably.

In a study of 145 stalkers who were sent for psychiatric treatment, Mullen et al. (1999) found that 77% of the studied stalkers had previously threatened their victims before carrying out the assault on the victim. Though they acknowledged their clinical study included stalkers with obvious mental disorders, they too concluded the most likely victim of stalking is an ex-intimate partner, and the most likely assailant of physical assault is a rejected ex-intimate partner stalker.

Senkans et al. (2017) attempted to better define the connection between intimate partner violence and stalking after a relationship has ended. The term postrelationship stalking used in their research is their attempt to stop the conflation of intimate partner violence with postrelationship stalking. They argue though the two ideas are connected, there is a need in the literature to define and separate the two. They clarify that intimate partner violence happens during a relationship and postrelationship stalking happens after the relationship is over. Postrelationship stalking occurs when one party ends a relationship and no longer desires contact, but the other party engages in repetitive behaviors and continues the unwanted contact. In their study of 422 Australian undergraduates, Senkans et al. (2017) found 60% of males who engaged in severe intimate partner violence also stalked their ex-partner, and 61% of female intimate partner violence victims reported they were later stalked by their ex-intimate partner.

Intimate Partner Stalking and Intimate Partner Homicide

Rai et al. (2020) explain an intimate partner homicide is an incident where violence or the threat of violence from one person against their current or former intimate partner results in the death of one or more people. Stalking has been found to be a correlate of violence toward women, especially connected with homicide and attempted homicide among women (McFarlane et al., 1999). Monckton-Smith (2020) notes males vastly exceed females as homicide perpetrators and homicide victims except for intimate partner homicides where 82% of the victims are women.

McFarlane et al. (1999) reviewed homicide and attempted homicide cases of 208 women where 141 were killed at the hands of an intimate partner and 65 survived an attempted murder by their intimate partner. Stalking behaviors, including being followed or spied on at home or at work and undesired phone calls, were reported during the prior year in 76% of the fatal encounters and 85% of the attempted encounters. Also noteworthy was that during the prior year, in 67% of fatal encounters and 71% of the attempted encounters, physical intimate partner violence was reported to have occurred.

In the 1999 study by McFarlane and colleagues, informal sources were used to obtain information on the homicide victims, and informal sources for those women who experienced physical intimate partner violence, 89% of them also experienced stalking behaviors before the homicide. Victims who suffered physical intimate partner abuse prior to their homicide were very likely to have experienced stalking as well. Of the attempted homicide victims who reported physical intimate partner abuse in the year before their incident, 91% reported experiencing stalking as well. Also significant is their indication that ex-intimate partners were more likely to be the perpetrator of homicide and attempted homicides.

In a second expanded study, McFarlane et al. (2002) reported the cases of 821 women. Of these, 263 were victims of intimate partner homicide, 174 were victims of attempted intimate partner homicide, and 384 were either physically harmed or threatened with violence but did not suffer an attempted homicide. The 384 physically harmed or threatened women served as the control group in the study. This study found women who were victims of attempted homicide, in the year prior to the attempt, 68% were stalked and 69% were physically assaulted by an intimate partner. When they included stalking as a part of the definition of intimate partner violence, they noted 85% of the women were also victims of intimate partner violence before the actual or attempted homicide. Also, intimate partner violence and stalking were shown to be associated as in 79% of the homicide and attempted homicide cases, the victims were stalked.

Another study reviewed cases of intimate partner homicides. In this study, Rai et al. (2020) looked only at cases where a homicide was committed by an intimate partner who stalked. A history of abuse was only documented in fewer than 20% of the cases. This further strengthens the argument that victims do not disclose their abuse to formal sources.

Cited as the most significant finding in their research was that the use of a firearm by a suspect doubled the likelihood of an intimate partner homicide caused by stalking. Furthermore, victims who had reported past abuse were found to be three times as likely to be a victim of intimate partner stalking precipitated homicide.

Monckton-Smith's (2020) research suggests intimate partner violence may be a sudden crime of passion and suggests an eight-stage progression of behavior involving intimate partner homicide. She suggests talking is part of an escalation in an intimate partner's attempt to control or regain control of a victim. In a review of 372 cases where a male killed their female intimate partner, the perpetrator showed stalking behaviors by gaining intelligence about their victims and imparting fear and anxiety against them. In cases where stalking was continuous, there was a high risk of homicide. She further notes that progress through the final stages is not quick, and interventions during that time could prove helpful in preventing intimate partner homicides.

Criminal Justice Response

With stalking that occurs along with domestic violence, the criminal justice response has been to treat the stalking behavior and address it legally under domestic violence laws rather than stalking laws (Melton, 2004). Melton conducted a survey to explore the effects legal intervention may have on future stalking behavior, the experiences of victims within the criminal justice system relative to stalking and domestic violence, and what a victim's desires are with the criminal justice system's response. The study found there is a lack of victim cooperation with the criminal justice system, legal intervention did not cause stalking to increase after intervention, and, although legal intervention does not necessarily cause stalking to decrease, legal intervention could cause a stalker's behavior to become less violent toward a victim.

Backes et al. (2020) also reviewed a range of criminal justice responses to intimate partner stalking and what of those responses have been successful in helping intimate partner stalking victims. In their research, a lack of victim participation was noted, however, complete cooperation and participation by a victim was identified as a factor aiding intimate partner stalking cases through the criminal justice system. Overall, the study also found police lack an understanding of the characteristics of stalking and the relationship of stalking with intimate partner violence. Also noted was both victims and the police do not notice stalking behaviors displayed by abusers. Furthermore, of particular concern to some victims is the belief that their stalker may retaliate against them should they utilize the criminal justice system. The research identifies some concern for stalkers who use the criminal justice system to counter a victim's use of the criminal justice system which could hinder prosecution of cases and successful progression through the system itself.

The response by police and the court to a stalking victim is also an issue. As noted by Melton (2004), victims commonly reported the system did not take their report of

stalking seriously, the police or the courts offered no assistance with the stalking complaint, or a criminal justice practitioner disrespected them in some way. In contrast, some victims did note positive police responses including providing contacts for additional services and programs as well as officers who took stalking complaints seriously. This suggests additional training and resources for criminal justice personnel could improve victim experiences of the criminal justice system as well as more favorable outcomes in stalking cases.

Conclusion

The connection between intimate partner stalking and intimate partner homicide is an even lesser researched area than the little researched topic of stalking itself. But there is a clear indication that women especially experience elevated levels of homicide by intimate partners specifically after threats of violence, actual violence, and stalking. Further research should be conducted to identify how early reporting of and early intervention in intimate partner violence and intimate partner stalking could prevent further intimate partner violence and any potential progression of an offender toward intimate partner stalking or intimate partner homicide. Worthy of other research would be identifying what effects steadfast participation by intimate partner violence victims and stalking victims in the entire criminal justice process would have on reducing intimate partner violence and intimate partner homicide. Additional research suggested by Backes et al. (2020) includes identifying how the response by the police of reported stalking victimizations could prevent future stalking victimization. Finally, Melton (2004) placed importance on giving victims a voice and allowing them to provide specific feedback on what they thought about how experiences with the criminal justice system could improve. There is certainly room for additional research on how the criminal justice system can improve for victims.

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ESSAY: “DRIVING INTO THE HEART OF THE NIGHT”:
REGENERATE MODERNISM IN THE WORK OF VIRGINIA WOOLF

TABLE OF
CONTENTS ↑

In *A Room of One's Own*, Virginia Woolf describes her ideal of the shaman, and it turns out to be the same shaman as those depicted on cave walls ten thousand years ago: the gargoyle-like half-man/half woman, or half-human/half-beast, always half-something mixed with half-something else: a walking liminal zone. Woolf's shaman, also, is the one who has not only been at the margin with Otherness but who has become the margin between male and female: the androgyne. “In each of us,” she writes in *A Room of One's Own*, regardless of physical gender, “two powers preside, one male, one female.” Unfortunately, the male power occults the female in men and the female power marginalizes the male in women—but, “[t]he normal and comfortable state of being is that when the two live in harmony together, spiritually co-operating.” Woolf refers to Coleridge's conviction that superior minds are androgynous, for “[i]t is when this fusion takes place that the mind is fully fertilized and uses all its faculties” (Woolf *Room* 98). She herself feels that “[p]erhaps a mind that is purely masculine cannot create, any more than a mind that is purely feminine ...” and that “the androgynous mind is resonant and porous; ... it transmits emotion without impediment; ... it is naturally creative, incandescent and undivided;” and, most significantly, that the androgynous or mature mind “does not think specially or separately of sex” (98-99), and that “without some mixture of the [male and female] the intellect seems to predominate and the other faculties of the mind harden and become barren” (103-104). Woolf here explicitly acknowledges the creative/recreative necessity of the internal, psychological limen—and her themes and characters agree too.

But if her characters agree—if they come to resemble the androgynous mind—why does Woolf so often kill them? The simple answer is that death, unfortunately, was often a part of life as Virginia Woolf knew and experienced it. Death, also, was an ever-present part of the everyday practices associated with perpetrating British Global Imperialism. As represented in Woolf's literature, however, (as opposed to the murderous results of real Imperialistic agenda) fictional deaths are represented almost as the cost of (or even the reward for) redemption from the living death that was English society. Fictional death is, after all, not real; its portrayal is a convergence ritual which (re)creates death and suicide to soothe agonistic fervor and to prevent the outbreak or continued occurrence of the real thing. In other words, the purpose of the death theme in Woolf—and the theme of avoiding living-death as represented by most of the “surviving” characters—is not to promulgate continued clash with Other thought and ideology (although, ironically,

literature has done just that in patriotic and/or religious context, as with the case of Imperial apologist Rudyard Kipling), or especially not to comment on the death waiting for those who openly encounter the Other (both of which are readings which could and have been done) -- no, indeed: the theme behind Woolfian Modernism is of merger with Otherness, and of the death which comes if one does not merge. This theme strays far from the Western mentality of power, but both versions are general Modernist themes— maybe the Modernist theme, though it has been largely ignored. But for Woolf, especially, continued resistance to the coming of creative knowledge (as represented by convergence with Otherness) would only ensure the continued decadence of English culture, and every crazily “sane” Englishman would go on stumbling zombie-like through his graveyard of outmoded cultural motifs, and every sanely “crazy” Englishman would die, being too alive to live among the living dead.

Images of this social and individual English decadence occur throughout the Woolf canon, but we'll look at two books in particular: *The Voyage Out* and *Mrs. Dalloway*, from ten years later. *The Voyage Out* examines an English expatriate group in South America, cooped together inside a taxonomized hotel and surrounded by the firmly differentiated Otherness of South American nature and society. Characters drone on and on about their practice-lives, mulling over unconsummated relationships and longings for the gumption to follow any true-life impulse. They are the self-domesticated, socialized into a lifeless existence, paralyzed by fear of mere desires to relate to social exteriors. (Evince the man, Flushing, who said he “would not marry because most women have red cheeks, ... and would not eat meat because most animals bleed when they are killed” [Woolf *Voyage* 181], or Helen, “who admired the morality of youth, and yet she felt imprisoned,” who “escapes” having to think of a way out of her prison with busy-work, her embroidery, just as her husband escapes from thought with, ironically, books [190].) In Woolf's famous metaphor, the English are moth-like beings, kept from accomplishing any natural fate by the dry ethics of civil society, an impenetrable divide represented by the glass of the electric light bulb between a night moth and the light source the moth seeks. Wouldn't the naked flame be better? As perishing as that fate might prove, it is unnatural to keep from it, irrational to preserve life at the expense of it.

Midway through the novel a dance is held. There are civilizing rules, as always, but the dance is still a time of allowances made, of slight gaps in the chainmail that is the English social fabric. The windows of the hotel are thrown open and some essence enters in, resulting in some spiritual movement by some individuals. But when the sun begins to rise revealing the outside people become aware of their over-exposure to it; the openness ends, though the electric lights are even said to “prick the air very vainly.” “How silly the poor old lights look,” they observe. “And ourselves; it isn't becoming” (Woolf *Voyage* 153). Self-conscious pre-maturity catches up with them, and all movement ceases; it's one step forward two steps back for many, but not for all; for Rachel, Woolf's hero in this book,

something inalterable occurs. The man Rachel falls in love with, Hewett—the androgynous man who “should hate cutting down trees” (177) (domesticating the forests being a sign of the colonialist), and who has “something of a woman in him” (234) -- also shows definite movement toward maturity.

In Mrs. Dalloway, a similar cast plods its way through a predictable day; even what should be unpredictable, a suicide, causes no ruffle in the taut social fabric of London society. One of the two shaman of this novel (the second and most important of which we’ll come to later) appears amid the city’s deadness and pavement with a “voice of no age or sex, the voice of an ancient spring spouting from the earth,” speaking “with an absence of all human meaning”:

Through all ages—when the pavement was grass, when it was swamp, through the age of tusk and mammoth, through the age of silent sunrise, the battered woman ... stood singing of love—love which had lasted a million years, she sang, love which prevails, and millions of years ago, her lover, who had been dead these centuries, had walked, she crooned, with her in May.
(Woolf *Dalloway* 80-81)

Life hasn’t changed even if it has been paved. Here is a fantastic, an unreal moment—a moment having no beginning or end but happening eternally in a place where very little seems to happen outside the linear measurements of Big Ben’s hourly bonging. Someone, then, survives outside the trap of time, time being the prison we have constructed for ourselves. Just as the Universe doesn’t (as Aristotle declared it did) construct itself on binaries, time doesn’t exist in linear measurement—Einstein proved it; Woolf already knew. Is it wave-like then, curling over on itself? Apparently, the evidence is everywhere, in all things; who needed Einstein, really? Woolf didn’t. How authoritative, then, could all the even more transparent social conventions have been for her? the lockboxes of us and them, good and bad, male, and female, etc.? Not very.

In her novels Virginia Woolf went beyond equalizing opposites. She harmonized the strictly cleaved binaries, overcoming the conflict at the center of her own English culture’s reaction to Difference, and she did so by merging Englishmen with it. The death of her heroes, her shamanic characters, does often occur in Woolf’s writing—but for a living reason. It’s teaching violence, based on heading off the real thing by pointing out social flaws. Just as both ancient and modern pre-agricultural societies understand their ritual and artistic representations as just that: representative—so do the artists of ancient and modern post-agricultural societies (so-called “civilizations”); a ritual battle between two pre-industrial tribes would be understood metaphorically and understood as a means of disempowering a building tension—like dragging Jung’s Shadow out into the light, thus shriveling it. Through play, a bloodbath is avoided. Even in our modern world we have the release of Olympic sporting events and rugby and football, and very seldom does the

violence on the regenerate field of play “bleed over” into the stands. The violence portrayed in Woolf’s fiction carries on this ancient tradition.

The central shaman in *Mrs. Dalloway* is Septimus; he, like the old singing woman, is ignored, palliated by and filed away in the box labeled: crazy. Woolf speak about insanity with some authority since, by her own acknowledgment, she herself lived at the threshold of “sane” and something beyond. ... Septimus kills himself because he was alone, “alone with the sideboard and the bananas. He was alone, exposed on this bleak eminence, stretched out—but not on a hill-top; not on a crag; on Mrs. Filmer’s sitting-room sofa. ... There was a screen in front of him. ... Where he had once seen mountains, where he had seen faces, where he had seen beauty, there was a screen” (Woolf *Dalloway* 145). Septimus had been to war, had been forced traumatically outside the screen of social convention—but he had seen things there, formed inter-relationships with his fellows ... and now it was all back behind the screen. What would you do? Holmes, the representative of humanity’s impulse to self-protection (even when that protection has over-stepped all reasonable necessity and is doing more harm than good), has won. “But even Holmes himself could not touch this last relic [Septimus] straying on the edge of the world, this outcast, who gazed back at the inhabited regions, who lay, like a drowned sailor, on the shore of the world” (93).

Septimus’ death serves a purpose: something regenerative passes from him to Clarissa Dalloway, just as that something also passes to us, the readers. As the only one who is in the least affected by the old shaman’s death, Clarissa’s affectedness builds. She begins by musing on her feeling “odd affinities” with strangers met, even with trees, and comes to a “transcendental theory” of an unseen, ghostly self, which “must survive” death and is “somehow attached to this person or that” (153). The effect of Septimus’ death climaxes when Clarissa becomes inhabited by a realization which might be described as the androgynous ghost of the old singing woman and Septimus himself, as if Septimus upon his own death, transferred into her, shamanizing as well as androgynizing her.

A thing there was that mattered, a thing, wreathed about with chatter, defaced, obscured in her own life, let drop every day in corruption, lies, chatter. This he [Septimus] had preserved. Death was defiance. Death was an attempt to communicate; people feeling the impossibility of reaching the center, which, mystically, evaded them; closeness drew apart; rapture faded, one was alone. There was an embrace in death. (184)

And so, the marginal-that-should-be-the-central dies, but his death “communicates,” empowers Clarissa, also marginalized—and she survives, and she knows. Septimus, who should have been the center to fill the “lack” at the decentered structure of English society, was marginalized—and English society had no idea that the real power was at the margins. This is Modernism: the center may no longer exist, but its power has passed to the margins; in Modernism, the marginal is the powerful.

It is the same with Rachel's death in *The Voyage Out*. After gaining shamanic knowledge (a scene which we will soon discuss) she sickens and dies. And though most of the English stay behind their boxes—their hotel and their distractions, their busy-work, and their barren bantering—Hewett doesn't: he's gone, and he remembers. "Never again would he [Hewett] feel secure; he would never again believe in the stability of life or forget what depths of pain lie beneath small happiness and feelings of content and safety" (Woolf *Voyage* 326). He's grown up, matured beyond his entire culture. Small happinesses, contentment, safety: these are not real; these are illusions. Believing in them, selfishly pursuing them, is a waste of actual life. Hewett will be marginalized for not believing the illusions, but he will carry the knowledge forward and he will pass it on, for that is the real way the Universe constructs itself: in this cyclical inter-related fertility.

Beyond her purpose of defining Modern society's potentially suicidal flaws by revealing through symbolic death its "lack" of center, Woolf's writing also gives solutions. If in her books, the ruling center of English (and Western) culture is, in fact, a lack of a true ruling center, then the West can no longer be considered the center of anything at all; in other words, the Anglo-Saxon Patriarchy, who think itself to be in control of women, of Empire, of nature, of itself, is not actually in control of any of these—not even or especially not the last. The portrait of Western Imperialism as an evil inhumanity having its oppressive way with a child-like world is stereotypical Modernism, but here's the deeper theme that's too often missed: Woolf (and many other Modern writers, albeit to varying degrees) vividly describes an outside world (the world outside of the Western, homo-social in-group) far different from that powerless-but-noble marginal world said to be described (Dickensized, if you will) in Joyce, Conrad, Woolf, etc. Indeed, marginal Otherness, it turns out in Woolf, is found to have been no more than superficially wounded by Colonialism—and scarring nicely, thank you, if it was hurt at all; nature is regenerating at its stoic leisure; pre-"civilized" societies are as "dangerous" as ever to civilization; even civilized (read marginalized) English women are still (as women at least, if not as politically powerful persons) integrally intact, if not, moreover, bemusedly detached from the mistakes of literalism made by their self-emasculating men.

Which brings us to what the powerful margins of Western culture are busy doing out there. They are turned outward, saving the soul of the West. Clarissa and Septimus, as already delineated, express a knowledge of their inter-relatedness with others outside themselves and outside the stifling culture they are trapped inside. *The Voyage Out*, however, includes what may be one of the first artistic depictions since the Middle Ages of Westerners actually being subsumed into an Other culture group. Paradoxically, the scene occurs at probably the instant Rachel is infected with the disease which will kill her. With Rachel are a small party of English, including Hewett. They departed their boat (after a Conrad-like trip into the depths of the forest) and stood at the margins of the forest, which "echoed like a hall. There were sudden cries; and then long spaces of silence, such as there

are in a cathedral” (Woolf *Voyage* 253). All but Rachel and Hewett stopped at the “verge of the forest” (a cathedral chock with the intermittent crying of ... gargoyles?), armed with books and paints, for “protection against boredom,” or against everything but (254). “As [Rachel and Hewett] passed into the depths of the forest the light grew dimmer, and the noises of the ordinary world were replaced by those creaking and sighing sounds which suggest to the traveler in a forest that he is walking at the bottom of the sea” (256). A connection is made inside, both between the two lovers and with some infection. They get lost for a time, but find their way back, only to find the others even further back, in the boat, with Hirst complaining, “Those trees get on one’s nerves—it’s all so crazy. God’s undoubtedly mad. What sane person could have conceived a wilderness like this, and peopled it with apes and alligators? I should go mad if I lived here—raving mad” (260). His words drip with irony, for, as we’ve seen, the truth is that Hirst is the crazy one, among those mass of men whose greatest fear is going sane.

The boat continues into the dark heart of the forest where finally the group encounters a native village. A sublime scene unfolds, cued by a passage reminiscent of what would become Virginia Woolf’s signature interior monologues and imagistic word-painting. At the climactic moment of this Inter-cultural meeting, Flushing advances to a center between the two groups, there joining from the Other side “a lean majestic man, whose bones and hollows at once made the shapes of the Englishman’s body appear unnatural” (269), as if a domestic cow were standing beside a wild eland. The two groups are mesmerized for a while, piqued by their differences, “but soon the life of the village *took no notice* of them; they had become absorbed into it” (269; italics mine). This allowance made by the natives, allowing the Other nearly immediate and free access to their community, reveals a non-difference-making culture, a non-agonistic psychological foundation—which, of course, make them very vulnerable to the English mentality of power. Here is the sad the sad history of the world: a culture opens itself freely to the West, and soon the West destroys that culture from within. like termites or a disease. That Colonialism is wrong to exploit this “weakness” is a recognized Modernist theme, but Woolf’s goes further here, citing Other culture as not weak but better, as something to work toward. This is a currently popular theme that hadn’t been seen in millennia before the Moderns reclaimed it. And, in the words of Hewett, “it makes us seem insignificant, doesn’t it?” (270).

The mass of the English group ends up feeling “exposed,” feeling they had “ventured too far,” but not the individuals of Rachel and Hewett; they feel that they have gained some transcendent truth of the inherent “pain in happiness” (270). In Woolf’s work, we can conclude that even as the inflated Self of Anglo-Saxon manhood stands, so to speak, in flaccid effigy of the Shakespearean portrait of androgynous English-Man (a shriveled Lear, Hamlet, Richard II, etc.), it is the open, non-agonistic, androgynous individual (whether or both male and/or female) that crosses beyond the influence of soul-

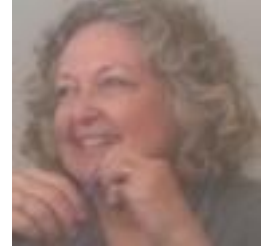
leeching social constraints. And it is at these places beyond where, for Woolf, the true center can be found: on the margins with those at the limen with Otherness, gaining valuable experience and insight. Upon their return (just as Plato's escapee from the allegorical cave of shadows is compelled to return, to bring back the boon of knowledge of the light) Woolf's escapees are still, sadly, ignored and alienated, even to the point of death in a case of "pearls before swine." (As, indeed, in the case of Septimus, "who was the greatest of mankind ... lately taken from life to death [the living death of life back behind the oppositional screen], the Lord who had come to renew society, the scapegoat, the eternal sufferer" (Woolf *Dalloway* 25).) But in Woolf's art it is these dead who prove more alive than the living; it is they who were beyond the oppositional, agonistic screen into exterior Otherness, they who, ignored and devalued, deem unlivable the barren existence back behind the interior screen of sterile Imperialism. It is this message, this teaching-death, that survives and communicates.

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SHORT ESSAY: THE INFLUENCE OF HISTORY ON THE CHARACTERS IN *NO ONE WRITES TO THE COLONEL*

TABLE OF
CONTENTS ↑

Gabriel Garcia Marquez's novella *No One Writes to the Colonel* examines the experiences of an elderly retired colonel who is awaiting his pension check from the government to support his wife and himself in their last years. The colonel and his wife live in Colombia, and he served in the revolutionary military during the beginning of the twentieth century. The colonel has been waiting patiently for his check for fifteen years and believes the check will one day come, despite the constantly changing political figures in power. Using the theory of New Historicism, we can identify how Garcia Marquez's novella was influenced by the culture and events he grew up witnessing in Colombia. The main character, the colonel, along with his wife, were shaped by the limitations imposed on them by both living in an area with constant civil conflict as well as the cultural, gender-related expectations of Latin America during this time.

In *No One Writes to the Colonel*, the civil wars in Colombia are referenced multiple times since the plot of the novella revolves around the colonel awaiting his pension check for his past military service. The setting of this narrative is in Colombia during martial law after many years of constant violent conflict, termed *La Violencia*. This era of violence "caused murders, massacres, and general destruction in certain places. Most of the victims were peasants" (Sanchez 154). Years of systematic violence takes a toll on a country's residents, which is showcased by Garcia Marquez with the current circumstances of the colonel and his wife. Eventually, "In June 1953, General Rojas Pinilla staged a military coup and the violence escalated, leading to the fall of the military regime and the birth of the *Frente Nacional* in 1958 ... The *Frente Nacional* agreement ended *La Violencia* but did not eradicate guerilla groups and excluded the Communists and other leftist parties from the government" (120). Presently, the small town where the colonel and his wife live is controlled by the police, including censorship and curfews. The colonel's only son has been killed in a rebellion incident. There are limited job opportunities available for the elderly couple with no other family to lean on, so they have resorted to taking care of their late son's rooster in the hopes that the rooster will win in a cockfight; the colonel and his wife could live for several years on the winnings. The couple take care of this bird even though they are almost starving themselves and are selling any possessions that have value to afford food. Garcia Marquez includes these day-to-day experiences of the colonel in a slow pace that represents the monotony experienced when a village is dominated by the police and the actions of its inhabitants are restricted, including economic opportunities.

War in Colombia was a frequently reoccurring event, so living with the aftermath of conflict is a theme within this novella that represents the citizens of Colombia both when Garcia Marquez was growing up and in the era in which the novella is set; Gabriel Garcia Marquez was born in a coastal Colombian town in 1928 and spent his formative years in Colombia (Maurya 55). The colonel has made it to an advanced age, but Garcia Marquez implies that this is not the most typical outcome. When getting dressed for a funeral, “‘This burial is a special event,’ the colonel said. ‘It’s the first death from natural causes which we’ve had in many years’” (Marquez 6). Violence-related death has become so normal for the people of Marquez’s fictional village that it is unusual for someone to die naturally. Garcia Marquez includes this anecdote to further show the reader the impact that systematic violence has on the ordinary people in the middle of violent conflict. Garcia Marquez does not actively support or condemn the current political party in *No One Writes to the Colonel*; he merely demonstrates the systematic oppression that is imposed on regular citizens when there is political turmoil. In such, he is criticizing the government’s inability to take care of its citizens. The colonel has been waiting fifteen years for a check that he has faith is coming, but as his lawyer points out, the colonel’s paperwork has probably been passed through an incalculable number of hands and there is no telling where it is now with the overturn of staff in the Ministry (26). The colonel’s faith that he will receive his check from an unstable government is poignant, as that same government is unlikely to care if the colonel receives the money he is owed.

However, Colombia was not the only country in Latin America where the violence impacted its citizens, and further, its authors. Other countries, such as Cuba, were experiencing similar events and with that, “The Cuban Revolution had a tremendous influence on the writers and intellectuals of Latin America. The literary world witnessed a definite process of polarization between progressive and conservative trends” (Maurya 55). Garcia Marquez used the attention brought to Latin America to show the plight of the average villagers who were caught within the uncontrollable forces of political discord. He gave a voice to the people of Colombia, not just the politicians and combatants who were making the international headlines. The characters of the colonel and his wife were familiar to readers not just in Latin America, but all over the world; the characters were trying to make the best of a situation they had limited control over.

The colonel and his wife also both operated under the cultural norms for their respective genders. The colonel feels that it is his responsibility to provide for his wife and himself. It was only in 1945 that women in Colombia were granted recognized citizenship from the government (Gonzalez 703), so the colonels’ wife has been dependent on him for their entire marriage. The colonel’s wife often pressures the colonel to sell the rooster, but ultimately concedes to the wishes of her husband, as their relationship dynamics reflect the traditional gender roles of Latin America during this era. The colonel’s wife says, “I’m tired ... Men don’t understand problems of the household. Several times I’ve had to put stones on to boil so the neighbors wouldn’t know that we often go for many days without putting on the pot (Garcia Marquez 41). It is her job to take care of the household, but she is struggling to manage with their limited resources. Garcia Marquez wrote the character of the colonel’s wife to be submissive to her husband, as was expected for Colombia during this time. There are multiple attempts where she tries to make her wishes and opinions known to her husband, yet he makes the final decision. During a disagreement between the

colonel and his wife, lightning and thunder occur and Garcia Marquez writes, “‘That’s what happens to you for not holding your tongue,’ he said. ‘I’ve always said that God is on my side’” (42). Even after the dissolution of Spanish colonization, Colombia was heavily influenced by the Catholic Church and its male dominant social order (Gonzalez 691). Their marriage is not an equal partnership, which limits the colonel’s wife in how she can help their plight. Garcia Marquez incorporates the character of the colonel’s wife to provide a foil to the colonel within their gender roles, which highlights the cultural expectations each partner has within their marriage, as well as the narrative.

In *No One Writes to the Colonel*, Garcia Marquez describes the experiences of an elderly couple who have limited control over their realities. The colonel and his wife are restricted in their daily lives by the rules of martial law and the cultural gender roles of Latin America during this era. Garcia Marquez used this narrative to give the reader insight into the impact that years of violence has on citizens whose main goal is just to survive, and how even if a war is over, the aftermath can manifest into years of struggle for its survivors. While the colonel and his wife are fictional characters, they are representative of the real people who experience these events.

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OVERVIEW: PHARMACEUTICAL ADVANCES IN COMBATING COMMON COLD, HERPES AND INFLUENZA

TABLE OF
CONTENTS ↑

Abstract

Humans are habitually susceptible to pathogenic bacteria, infections and specifically viruses. The immune system can be compromised with the slightest amount of pathogenic interaction that can cause a numerous amount of side effects and conditions. There are many pathogenic viruses humans can experience in their lifetimes and the most common ones are the viruses causing influenza, herpes and common cold. There are three types of the Influenza virus: influenza A, influenza B, influenza C, two types of herpes simplex viruses (HSV-1 and HSV-2) and several types of rhinoviruses that causes the common cold. Is it possible to create a vaccine that can effectively treat each type of infection? Moreover, the nature of most viruses is prone to mutate frequently making creating a vaccine that can treat mutated strains of the virus difficult. While creating a one pack vaccine to prevent against these diseases may not be possible, there are several antiviral drugs produced by the work of brilliant scientists to combat these viruses. This article provides an overview of the antiviral drugs used in the treatment of viral infections and their mechanisms of action in halting the replication of these viruses in human body.

Introduction

The main causal agents for human illnesses are viruses and it has been estimated that viruses produce four times as many illnesses as bacteria. It has also been estimated that each year about 90% of the US population is affected by one or more upper respiratory infections such as the common cold, herpes, and influenza [1]. While in most cases these viral infections are self-limiting requiring no extensive treatments, some could lead into a secondary infection which could cause substantial morbidity. With the ever-increasing prevalence of these common viral infections and other chronic viral infections such as HIV and Hepatitis B and C, there has been an increasing demand for the antiviral drugs. Despite the complex processes involved in the development of antivirals, research in the past decades have brought many antiviral drugs for clinical use and found to have excellent efficacy in the treatment of viral infections. This review article commemorates some important antiviral drugs used in the treatment of the common viral infections such as Influenza, herpes and common cold along with their mechanism of action in inhibiting the viral replication.

The Common Cold

The common cold is an infection that has been prevalent since the beginning of history [2]. Although figures differ, it is estimated that young children have around five to eleven respiratory infections per year, while adults are expected to have two to four respiratory infections [3-4]. Although there is no standard definition for the common cold due to variations in the symptoms, the common cold is typically seen and classified as an

upper respiratory tract infection caused by virus or bacteria [2]. Upper respiratory tract infections affect the sites including the larynx, nasal cavities, nasopharynx, oropharynx, throat, sinuses, conjunctiva, and inner ear. Symptoms of the common cold are characterized by rhinorrhea, nasal congestion, sneezing, cough, sore throat, and a fever less than 37.8°C [5]. The common cold has been seen to have an incubation period of about one to two days and the symptoms typically are seen to clear up within one week. The estimated direct and indirect costs caused by the common cold amount to about sixty billion dollars each year in the United States alone [2-4]. There are many viruses that can induce an acute respiratory infection. In a definitive study conducted by the University of Turku, two hundred patients that demonstrated the symptoms of a common cold were studied over a ten-month period to find the agent causing their symptoms [6]. Of these two hundred subjects, only 138 viral etiologies were established. The results of the established viral etiology proved that HRVs are the main causative agent of the common cold, in which 105 of the subject's symptoms were caused by HRVs. The second largest causative agent of common cold symptoms was two different strains of coronavirus, which was only detected in 17 of the subjects. Through this study, HRVs were found to be the source of infection of more the 50% of the patients possessing the common cold [6]. A more thorough breakdown of the causative agents and the percentages can be found in Table 1. Through other studies, it has been estimated that HRVs are responsible from 50% to 80% of common cold cases [2]. Since rhinoviruses have been discovered to be the leading cause of the common cold, finding a method to prevent the effectiveness of its infection have been a central focus of curbing the common cold.

Causative Agent	Number of Patients	Percentage of Patients
Rhinoviruses	105	52.5%
Coronaviruses	17	8.5%
Influenza A and B	12	6%
Parainfluenza (Type 1-3)	7	3.5%
Double Viral Infection	10	5.0%
Viral and Bacterial Infection	6	3.0%
Miscellaneous Agents	7	3.5%

Table 1: Causative agents of symptoms of the common cold in a study funded by the Academy of Finland, Turku University Foundation, Sigrid Juselius Foundation, and Glaxo Wellcome, UK [6].

Human Rhinoviruses (HRV) are members of the Picornaviridae family and are under the genus of Enterovirus [7-9]. HRVs are non-enveloped, positive-sense viruses that consists of a single-stranded RNA genome, approximately 30 nm in diameter, within an encapsulated icosahedral capsid that consists of four viral proteins. The viral capsid contains narrow depressions called “canyons” around the 5-fold apexes [7-8]. The RNA within HRVs code for 11 distinct proteins [4]. Genetic sequencing and recent studies have proven that there are three distinct species categorized as HRV-A, HRV-B, and HRV-C [9]. With the current genome sequencing and serological methods, there has been distinctly named 83 types of HRV-A, 32 types of HRV-B, and approximately 55 types of HRV-C [4] (Figure 1). These varying types of HRVs have different physiological traits that causes varying degrees of virulence [10].

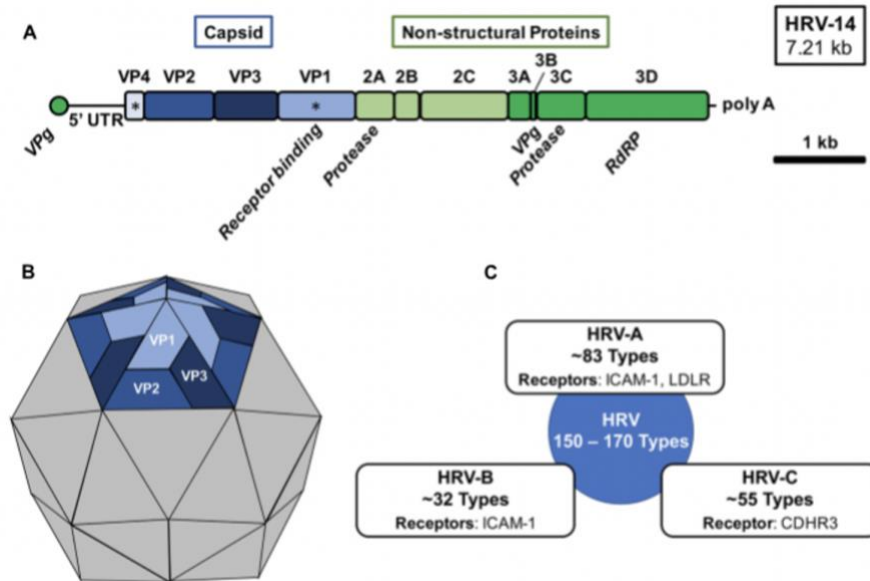


Figure 1. Genomic Organization of Human Rhinovirus

HRVs possess genetic variations as well as similarities in the processes of infection. HRV-A and HRV-B were classified into two different groups depending on usage of cell receptor for infection [9]. The differences in the genetic makeup of HRVs give them differing amounts of physiological traits. Strains within a specific HRV species will contain greater than 70% of amino acids commonality. Majority of HRVs have been found to grow best at temperatures of 33-35 °C, which limits the HRVs ability to reproduce within the lungs but makes HRV growth favorable within the larger airways. [10]. However, there has been three types of HRV-C (C2, C15, and C41) that have been identified to be able to grow equally well at the temperatures of 33°C, 35°C, and 37°C in vitro [10]. The ability to grow at temperatures up to 37°C is an implication that HRV-C may be more prone to cause more severe infections or lower respiratory tract infections [10]. Studies have shown HRVs have been linked to causing lower respiratory tract infections, including pneumonia, bronchitis, and bronchiolitis [6]. HRVs have also been proven to help induce lower respiratory tract infections such as pneumonia and bronchitis and have been seen to cause exacerbations of asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis [11]. Wheezing infection caused by HRVs in that of infants have been studied to have a strong correlation of developing asthma in that of predisposed children [11]. An increase of chance for secondary bacterial infection have been noted after having an initial infection with an HRV [12]. HRV-A and HRV-C have been associated to cause more severe infections and exacerbations than that of HRV-B species.

Due to the large variety of viruses that can produce the common cold, a vaccine would most likely be ineffective in building an immunity to all the serotypes of HRV. An effective vaccine and or treatment for the common cold would relieve 25 million people of upper respiratory tract infections a year and resolve a large portion of economic burden [2]. With the ubiquity of the common cold and the potential for HRVs to produce more severe respiratory tract infections and exacerbations of chronic lung diseases, a large medical issue would be resolved through an effective solution to HRVs. Previous attempts to

produce a HRV vaccine were made through the administration of a formalin inactivated single HRV serotype (HRV13) [9]. The administration of a monovalent vaccine was seen to produce a minimal protective effect and was quickly replaced with the testing of vaccination containing 10 HRV serotypes [10]. In addition, this vaccine was seen to not produce much of a cross-serotype protection leading to the assumption that the administration of inactivated HRVs as a vaccine are insufficient for producing broad protection. An effective HRV vaccine must produce protective neutralizing antibodies to potentially more than 150 serologically different species of HRV [4]. The search for this effective vaccine or treatment against HRV promises to be fruitful after searching for conserved antigenic site through multiple species [6]. Attempts to combat the infection of HRVs has resulted in the synthesis of active compounds to inhibit the infection of HRVs (Figure 2). These compounds are broken into three different types that aim to prevent HRVs from replicating: capsid-binding compounds, RNA synthesis inhibitors, and HRV 3C protease inhibitors [13].

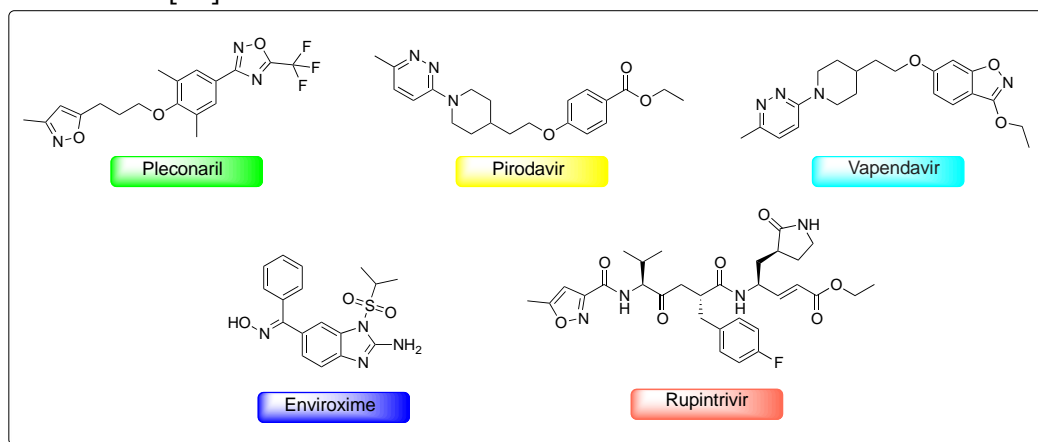


Figure 2. Antiviral drugs effective in the treatment of common cold

Capsid-Binding Compounds

One of the types of synthesized drugs that show promising ability to combat against the infection of viruses are capsid-binding inhibitors. Capsid-binding chemicals are effective because these chemicals bind to the canyon on the capsid of the HRV virus surface inhibiting the uncoating step by stabilizing the viral capsid dynamics. One of the frontrunners for a capsid-binder for combating against HRVs was pleconaril [8]. Pleconaril is an orally administered inhibitor of picornavirus replications which integrates into a hydrophobic pocket within the major coat protein (VP1). By inhibiting VP1, the functions of attachment to cellular receptors and uncoating of viral proteins are inhibited [14]. The administration of pleconaril in two phase III, double-blind, placebo-controlled studies demonstrated that pleconaril is effective in producing a more rapid loss of culturable virus [14]. Several studies testing pleconaril's ability to inhibit viral agents demonstrated overwhelmingly positive results; within three different studies, pleconaril produced an 87% effectiveness against baseline viral isolates, inhibited 89% of 46 different rhinovirus clinical isolates, and inhibited 92% of the 101 prototypical HRV strains (this study was conducted before the discovery of HRV-C). On the contrary to the positives to pleconaril, the postbaseline viruses harvest from the patients in the pleconaril demonstrated reduced drug

susceptibility at a higher frequency than that of the placebo group [14]. At least ten-fold reduced drug susceptibility was found in 10.7% of the postbaseline viral sample from the pleconaril-treated patients, while the placebo-treated patients demonstrated only 0.7%. Within Phase III of clinical trials for treatment of HRV in adult patients, studies for pleconaril were discontinued due to drug-drug interactions with oral contraceptives and insufficient efficacy in treating infections [15-16].

Pirodavis was another frontrunner of a capsid-binder chemical against HRVs. Pirodavis is a pyridazine derivative which is one of the most active capsid-binders against many HRVs in vitro [13]. Pirodavis was administered intranasally owing to the fact it undergoes ester hydrolysis resulting into an inactive acid derivate in vivo. Pirodavis was seen to provide protection against infection if administered before exposure to viral agents [13]. However, for Pirodavis to provide this effective protection, it had to be administered six times a day [17]. In addition to the inconvenient frequency of administration, the administration of Pirodavis reduce only the viral shedding during treatment [17]. Pirodavis produced no reduction of clinical signs and respiratory symptoms were observed and was associated with an unpleasant taste and an increase in the presence of blood in nasal mucus. Pirodavis's poor pharmacokinetic properties and its inability to produce sufficient clinical effect resulted in discontinuation of the study and use of Pirodavis [13]. A benzoxazole analogue of Pirodavis, known as Vapendavis (BTA-798), has proved to be a drug to treat asthma exacerbations induced by infection of an HRV. However, in 2017 it was reported that Vapendavis failed Phase IIb clinical trials [18]. Other novel capsid binding compounds have produced effective inhabitation against HRVs and may be candidates for future testing and development However, till date no drug to date that utilizing binding to the capsid of HRVs have been approved for clinical use [18].

RNA Synthesis Inhibitors

One effective drug to inhibit viruses are RNA inhibitors; these chemicals bind to the RNA of a virus, therefore inhibiting the replication of it. There has been a small number of compounds that have been tested and synthesized for the use of inhibiting the synthesis of the RNA of picornaviruses, although none of them have been approved for the treatment of HRV infection [8]. One compound that showed promise within this pathway of inhabitation was Enviroxime (LY122771-72) [8]. Enviroxime is a substituted benzimidazole derivative and is generally administered intranasally owing to gastrointestinal side effects caused by oral administration [19]. A detailed study on enviroxime's ability to inhibit HRVs in vivo produced disappointing results; A comparative study of enviroxime's effect against two types of HRVs demonstrated no ability to prevent infection nor reduce the frequency of infection and there was found no significant difference between the enviroxime group and the placebo group [14]. Due to these insignificant results produced by enviroxime, clinical trials were discontinued. The ineffectiveness of enviroxime may be due to the positive-strand RNA possessed by picornaviruses having a large variety of mutants that exist within a viral population [20]. In fact, picornaviruses are known to be able to easily overcome cellular or viral protein targeting compounds [20]. The variety of mutants allow for a rapid selection of those mutants that poses resistances for antiviral drugs attempted to be used [19]. It has been shown that an alteration of a single amino-acid within the 3A region within Poliovirus 1 and HRV-14 are sufficient enough to produce a resistant phenotype to enviroxime [19]. Later studies of enviroxime-like compounds were seen to be ineffective to

a resistant mutation that occurred within the hydrophobic domain of the 3A protein, supporting the idea that enviroxime binds with the hydrophobic portion of the 3A protein [20].

3C Protease Inhibitors

The last type of HRV antiviral drug to show promise are those that inhibit the 3C protease [8]. The 3C protease is crucial in that it is a complement to the 2A protease and contributes towards the redistribution of the nucleolin protein out of the nucleolus. One of the drugs that mimic the 3C protease inhibitors is Rupintrivir [7]. Rupintrivir possess an α,β -unsaturated carbonyl group and peptidyl-binding elements specific to binding for the 3C protease, which will undergo a Michael reaction in the presence of the enzyme catalyst Cys-147 [21]. This reaction results in a covalent bond formation which irreversibly renders the 3C protease inactive [21]. Within its original testing, Rupintrivir was seen to inhibit the replication of 48 different laboratory strains of HRV and 23 different clinical HRV strains in vitro [21]. Rupintrivir was formulated to be delivered intranasally [22]. When natural HRV infection studies were conducted in clinical trials, Rupintrivir was not able to significantly inhibit HRV replication and severity of infection, resulting in the termination of the clinical trials [22]. The inability to prevent natural infection could be, again, a result of the genetic diversity of HRVs and their ability to undergo mutations. However, a study conducted in vitro has demonstrated a slower rate of mutations within four different HRV serotypes (HRV2, HRV14, HRV29, HRV Hanks) when exposed to increasing amounts of rupintrivir [23]. This study demonstrated there was a slow accumulation of amino acid substitution with the HRV serotypes to rupintrivir, which demonstrates the potential upside of using a 3C protease inhibitor as an antiviral against HRVs [23]. Although not being productive against HRVs in natural infections, Rupintrivir has been seen to be effective against strains of enterovirus, a family also known to cause common cold infections, and is even considered a potential agent to treat EV-71 infections [23]. By this recent study, interest in producing other 3C protease inhibitors may escalate and help to produce more effective drugs. It is important to convey that till date, there has been no 3C protease inhibitors that has been approved for treatment for HRV infection [9]. Table 2 provides a comparison of these drugs in terms of mode of administration and clinical trial state.

Table 2: A Comparison of antiviral drugs used in the treatment of common cold

Name of Drug	Mechanism	Administration	State of Clinical Trials
Pleconaril	Capsid-Binding	Oral	Failed Phase III
Pirodavir	Capsid-Binding	Intranasal	Discontinued/Never Reached
Vapendavir	Capsid-Binding	Intranasal	In process for asthma exacerbations
Enviroxime	RNA Inhibitor	Intranasal	Discontinued
Rupintrivir	3C Inhibitor	Intranasal	Discontinued

The Herpes Simplex Virus

For as long as viruses and infections have been around, the herpes simplex virus has been infecting the inhabitants of this planet. While humans are the only known species to have two distinct versions of the herpes simplex virus, it is hypothesized that even before

humans began to be infected, other animals were also found to have a version of the herpes simplex virus [24]. The first recorded discovery of the virus in human beings is said to be made by the great philosopher of Greece, Hippocrates. He used the word herpes to describe the look of a person's skin who was infected with this disease [25]. As time progressed, more studies were done and the term herpes began to be used for two types of viruses, the Herpes Simplex virus and the Herpes Zoster virus. While the Herpes Zoster and Herpes Simplex viruses can both be categorized as part of the Herpesviridae family, they differentiate at the genus level. The Herpes Zoster virus being placed into the Varicellovirus genus and the Herpes Simplex Virus under the Simplexvirus genus [26]. In this article, only the treatments for the herpes viruses that fit under the Herpes Simplex Virus will be addressed. The two main viruses which will be examined are Herpes Simplex Virus One (HSV-1) and Herpes Simplex Virus Two (HSV-2).

Both Herpes Simplex Viruses are similar in the fact that they are viruses that contain DNA as their genetic material, and they replicate this DNA using a specific type of HSV polymerase [27]. Both viruses can be characterized as latent viruses meaning that they go through dormant life stages after an initial infection but are later revitalized to reinfect the host. Both viruses have also been discovered in asymptomatic hosts where the latency of the virus can last indefinitely, and it is unlikely that the either virus will likely ever be eradicated [27]. It is of significance to note that these viruses are difficult to be identified by the human immune system possibly because they are enveloped viruses, that coat themselves in portions of a host cell, or due to the viruses' ability to create fake receptors for the antiviral systems of a person's immune response to attack [27- 28]

The differences between HSV-1 and HSV-2 stem from the difference in the glycoprotein sequences that make up the genetic information of the virus (Figure 3). These differences are manifested in the regions these viruses attack as well as the ways they are transmitted. Herpes Simplex Virus One is primarily an oral disease that results in sores forming around the mouth, which can last for up to 14 days [26]. These cold sores as they are often called can be transmitted via oral contact through sharing items that touch the infected area or direct skin to skin contact of the infection. HSV-1 is also known to be responsible for eye infections that can cause blindness, but this is a rarer form of the virus. Herpes Simplex Virus Two is most associated with a genital disease. Sores that are like the ones found in HSV-1 are formed around the genital regions of the infected individual and last for approximately 14 days. As far as studies have shown, the only way of transmitting HSV-2 is through sexual contact [26]. This is the more common form of herpes when it is referred to as a sexually transmitted disease (STD).

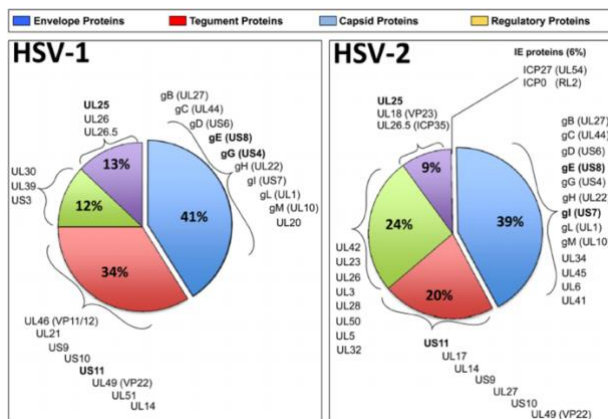


Figure 3: Comparison of HSV-1 and HSV-2 [29]

Starting in the mid-20th century, intensive studies began regarding possible treatments for Herpes Simplex Virus (Figure 4). While the drugs that resulted as part of the study have been shown to have continual positive results, there is still much to learn regarding the attacks of the virus and ways to completely rid an individual of it.

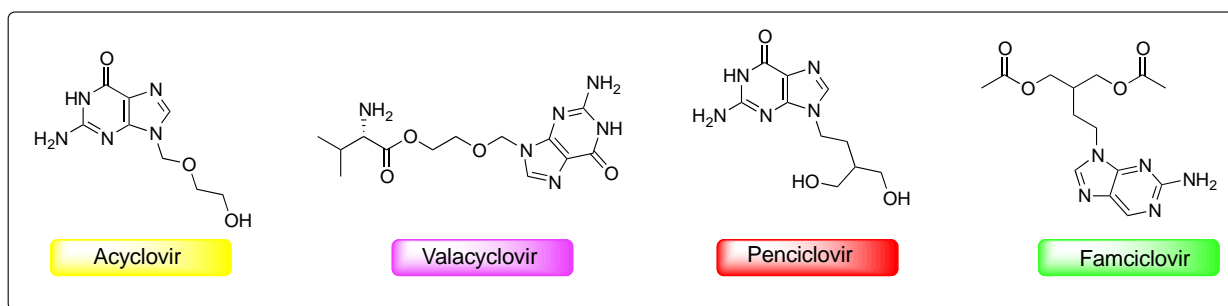


Figure 4. Frontrunner drugs in the treatment of Herpes Simplex

Acyclovir

Of all the drugs that have been discovered to treat Herpes Simplex virus, acyclovir was the first to be put to use. It was originally discovered in 1974, but it was not in clinical use until the year 1982 [30]. Acyclovir was the predominant drug used to fight against herpes until the late 1990's [31] although it is still in use today and is considered a very effective antiviral drug against both Herpes Simplex Virus One and Two (HSV-1, HSV-2) [32-34]. Acyclovir is an oxopurine that is guanine substituted by a (2-hydroxyethoxy)methyl substituent at position 9. Studies have shown that changing the substituents around Acyclovir results in a change in its effectiveness against the herpes virus [35]. In general, Acyclovir stops the genetic replication of Herpes Simplex Virus by stopping the HSV polymerase from continuing DNA replication. This occurs when Acyclovir produces its own type of UL30, a viral DNA polymerase, known as UL30ACV [36]. In order for Acyclovir to reach the genetic information of the virus, it first has to be monophosphorylated by the virus specified enzyme thymidine kinase [37]. Acyclovir monophosphate is subsequently converted to a triphosphate which is a more potent inhibitor of herpes virus DNA polymerases than of cellular polymerases (Figure 5).

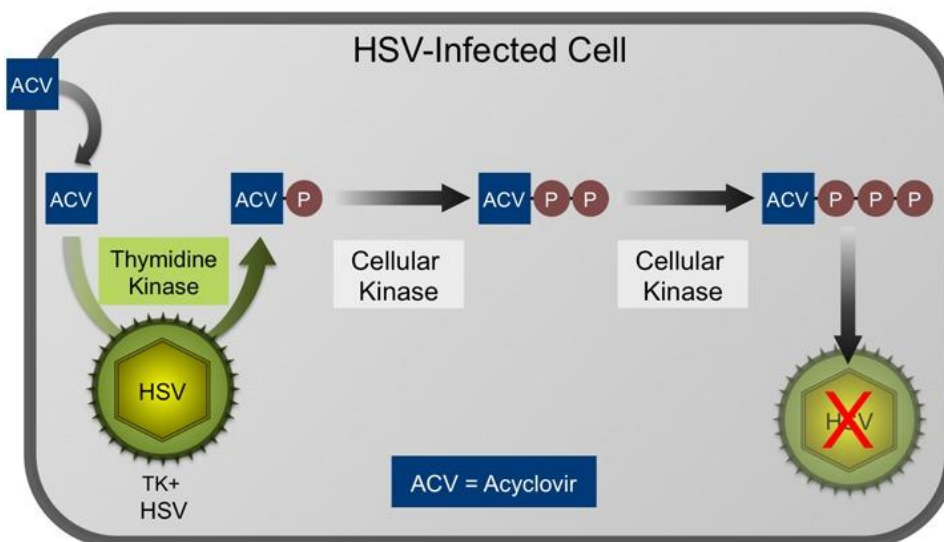


Figure 5: Attack Mechanism of Acyclovir

Herpes Simplex Virus (both HSV-1 and HSV-2) is generally treated with oral Acyclovir upon the first onset of the disease. This treatment generally lasts about a week before the symptoms begin to clear (Table 3). For treating a recurring case of herpes, similar dosages of Acyclovir are administered orally for only five days. In order to prevent the return of the disease, suppressive therapy is often given to patients, which has proven to be highly effective in impeding the return of the herpes simplex virus. Many of the side effects associated with Acyclovir, including problems regarding neurotoxicity are found when treating genital herpes. Intravenous treatment of the herpes virus is used when there is an inability to receive oral medication such as in neonatal care. Especially in patients that have compromised or developing immune systems, the effects of Acyclovir have shown to be extremely positive in fighting and stopping both Herpes Simplex Viruses, which is why it is still in use almost 35 years after its development.

Table 3. Drugs in the treatment of Herpes Simplex Virus

	Herpes Virus Outbreak	Brand Name	Application	Dosage Amount
Acyclovir	HSV-1: Cold Sores	Sitavig	Buccal Mucosa	50 mg adult
	HSV-1 and HSV-2: acute herpetic keratitis	Avaclyr	Ophthalmic Route	1 cm ribbon on eye
	HSV-1 and HSV-2	Zovirax	Topical Cream	Cover affected area
	HSV-1 and HSV-2	Zovirax	Oral/Intravenous	200 mg
Valacyclovir	HSV-1: Cold Sores	Valtrex	Oral	2000 mg
	HSV-2: Genital Herpes Initial Outbreak	Valtrex	Oral	1000 mg
	HSV-2: Genital Herpes Recurrent	Valtrex	Oral	500 mg
	HSV-2: Genital Herpes Prevention	Valtrex	Oral	500 or 1000 mg
Penciclovir	HSV-1: Cold Sores	Denavir	Topical Cream	Cover affected area
Famciclovir	HSV-1: Cold Sores	Famvir	Oral	1500 mg

Valacyclovir (Valaciclovir)

Valacyclovir is a L-valyl ester of Acyclovir. It is considered a prodrug of Acyclovir, which means that the drug basically behaves in the same way once it has been activated inside of the body [38] (Figure 3). This variant of Acyclovir was first discovered in the early 1990's as people began to search for ways to overcome some of the difficulties that came with prescribing Acyclovir. The distinct difference between the structural components in Acyclovir and Valacyclovir gives it slightly different properties. Soon after being discovered, it was introduced into use in the clinical setting and soon became the leading drug used to fight both Herpes Simplex Viruses. For Valacyclovir to be activated, an enzyme called human valacyclovirase interacts with the drug and specifically catalyzes ester prodrugs. Interestingly, this enzyme is found in the necessary organs of the body where the herpes virus needs to be attacked [38]. The catalyzation of Valacyclovir is practically the removal of the ester product leaving only the parent drug. Once the ester prodrug is catalyzed to form Acyclovir, the defense mechanism is the same [39]. The major reason that Valacyclovir began to be used in preference to Acyclovir was its increased effectiveness when given orally. Although Acyclovir had been a breakthrough in many ways, it was unable to properly infiltrate the body when administered through the mouth; however, Valacyclovir was found to be much more successful with oral administration to the point where it competed with the success levels of intravenous introduction of Acyclovir [40]. When compared to the oral administration of Acyclovir, the prodrug was shown to be three to five times more effective at entering the body and reacting with the Herpes Simplex Virus [40]. Not only was the oral application more successful, but studies have also shown that Valacyclovir resulted in a decrease in patient's pain levels faster when compared to its parent drug. These two factors as well as clinical tests show that Valacyclovir is the preferred drug in comparison to Acyclovir for patients with poor immune systems [41]. The increase in Valacyclovir's effectiveness also results in less administrations of the drug during the period of infection [41]. Even with the increased success found using Valacyclovir, there are still drawbacks related to the parent drug. One major drawback is the problem of neurotoxicity, which while it is still rare, is still evident in some cases [42].

In general, Valacyclovir treatment is very similar to the treatment methods of Acyclovir. The major benefit of valacyclovir over acyclovir is the fact that the medication has a lower effective dose. This means there are fewer doses needed for the patient to see the healing process begin [41]. Studies with valacyclovir have shown that a greater percentage of the drug is absorbed as compared to acyclovir. This leads to a lower dosage having a greater effect on the patient; therefore, it is considered a more effective drug. As with many viruses, there is a strain that becomes resistant to the antiviral drugs being used. After the introduction of Valacyclovir, strains of Acyclovir-resistant Herpes Simplex Virus were discovered in patients receiving treatment. In most cases, these resistant strains were found in patients with highly depleted immune systems [41].

Penciclovir

Soon after Acyclovir was introduced to the market, another drug was discovered to have similar antiviral activity regarding the Herpes Simplex Virus. Penciclovir, originally reported in 1985, was found to have similar properties when compared to Acyclovir and showed early potential for having a greater effect on the virus than its predecessor [43-44].

Like Acyclovir, the thymidine kinase in the infected organism's body plays a major role in the ability of the Penciclovir to affect the host [45-47]. Upon entry into the organism, the thymidine kinase will phosphorylate the drug allowing it to be converted into the necessary triphosphate form [45]. Once phosphorylated there exists a marked difference in the mechanism of action between Acyclovir and Penciclovir. While Acyclovir triphosphate is an obligate DNA chain terminator, Penciclovir triphosphate allows limited DNA chain elongation (short-chain terminator) by virtue of the 3' hydroxyl group on its acyclic side chain. One benefit of penciclovir was its high success rates in topical application. Primarily, Acyclovir and its prodrug, only yielded positive results when being introduced via intravenous or oral administration. However, the ability of Penciclovir to be used as a topical ointment gives this drug an ease of use that is not available with the other drugs examined [48]. The poor bioavailability of penciclovir led to the development of its prodrug famciclovir.

Famciclovir

Famciclovir is a prodrug of Penciclovir. Famciclovir is converted to Penciclovir via a 6-deoxy-penciclovir intermediate. This transition from prodrug to parent form occurs fairly rapidly [49]. The main benefit of Famciclovir is its effectiveness when administered orally. Famciclovir exhibits exceptional absorption and results in very little excess drug excreted after being given to patients. Downsides to the distribution of this drug has been found to be nothing outside of normal antiviral drug side effects. These include headache, nausea, and diarrhea [50]. However, these occurred no more frequently than those who took the placebo drug. Famciclovir has not been shown to have the neurotoxicity effects of other antiviral drugs used to treat the Herpes Simplex Virus. Famciclovir is primarily used as the oral treatment of penciclovir. It is given in the same dosage amounts and regimen as Penciclovir.

Influenza Virus

In 1918, a pandemic occurred that would steer the course of science and human history forever. The Spanish flu was an influenza pandemic that hypothetically originated in the trenches in Europe or in a small-town in Kansas [51]. This virus resulted in over 100 million cases and caused approximately 20-40 million deaths, primarily affecting those in their late twenties to early thirties. The Spanish Flu has been deemed the deadliest disease outbreak in modern history [52]. The result of this one virus has stemmed into several different strains such as the Swine flu and Avian flu. These strains are derived from a collective virus known as influenza A and there are three different types of influenza viruses: type A, B, and C. Influenza A viruses are the most virulent and they infect a range of avian and mammalian hosts. These venues are a direct result of respiratory transmissions and zoonotic transmissions. The specific strain of the influenza virus is known as H1N1 (Figure 6).

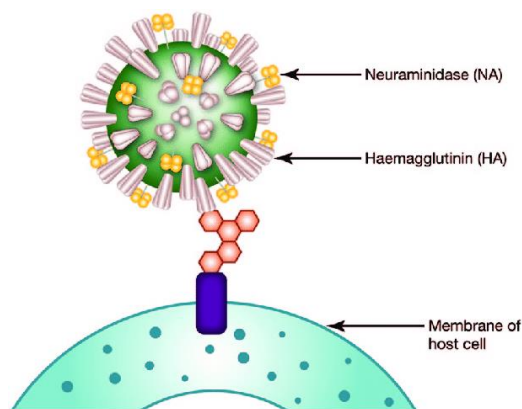


Figure 6: H1N1 Virus Particle [53]

The H1N1 virus particle is about 80–120 nm in diameter and roughly spherical. It is made up of a viral envelope containing two main types of glycoproteins hemagglutinin (HA) and neuraminidase (NA), wrapped around a central core that contains a single-stranded viral RNA [54]. Influenza virus NA is a receptor-destroying enzyme which cleaves the HA receptor, sialic acid, from a range of sialyloligosaccharides allowing newly formed viral progeny to escape the surface of infected cells and go on to infect more cells [55]. Infection by the influenza virus depends firstly on cell adhesion via the sialic-acid-binding viral surface protein, haemagglutinin, and secondly on the successful escape of progeny viruses from the host cell to enable the virus to spread to other cells [56]. To achieve the latter, influenza uses another glycoprotein called the enzyme neuraminidase, to cleave the sialic acid receptors from the surface of the original host cell [56]. Influenza virions have three surface proteins, the hemagglutinin (HA), neuraminidase (NA), and M2 protein. Influenza virus NA is a receptor-destroying enzyme which cleaves the HA receptor, sialic acid, from a range of sialyloligosaccharides allowing newly formed viral progeny to escape the surface of infected cells and go on to infect more cells [55].

Currently there are two classes of drugs that are licensed to treat and combat influenza: M2 and neuraminidase inhibitors, known as NAIs. Specifically, the NA inhibitors (NAIs) prevent release of newly formed virions from the cell surface. There are two NAI treatments for the influenza: Oseltamivir and Zanamivir. Both antiviral drugs (Figure 7) interfere with the spread of the virus from infected host cells by inhibiting neuraminidase influenza viruses [57].

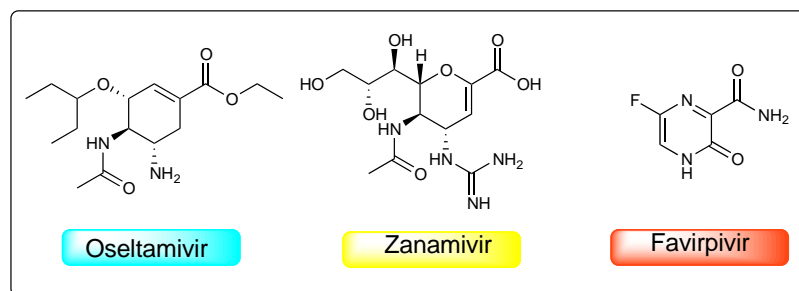


Figure 7. Antiviral drugs in the treatment of Influenza

Oseltamivir, commonly known as Tamiflu, is a phosphate salt one of the most popular orally available anti-flu drug, which is well absorbed and rapidly cleaved by endogenous esterases in the gastrointestinal tract, liver and blood to give OS carboxylate [58]. Zanamivir, otherwise known as Relenza, binds to the active site of the neuraminidase protein; rendering the influenza virus unable to escape hosts and infect others. In other words, the mechanism is the inhibition of the influenza virus neuraminidase with a possibility of alteration of virus particle aggregation and release [59]. Another antiviral drug used to treat the influenza virus is Avigan also known as Favipiravir. This anti-viral agent selectively and potently inhibits the RNA dependent RNA Polymerase, known as RdRP, of RNA Viruses [60]. Favipiravir is phosphoribosylated in the cells to an active form, favipiravir-RTP, which is recognized as a purine nucleotide by RdRp, and inhibits the RdRp enzyme activity [60]. All three antiviral drugs have shown promising results in treating influenza but can produce various side effects that should be taken into consideration.

Oseltamivir

In 1996, the Californian company known as the Gilead Sciences invented and patented a new miracle drug for both Influenza A and B virus known as Oseltamivir [61]. The drug was designed to be used for prophylaxis, prevention of disease and treating the flu. Soon after the discovery of Oseltamivir, it was soon purchased by a Swiss pharmaceutical company, Hoffmann-La Roche, for the rights to market the drug under the name Tamiflu (Table 4). Oseltamivir was then approved by the FDA for prophylaxis of patients one to 12 years of age, which is marketed by Chugai Pharmaceutical [62]. This antiviral drug has transformed countries that have been inflicted by numerous outbreaks.

The mechanism by which Oseltamivir operates can be shown in two separate ways: symptom relief and delayed onset. The mechanism for symptom relief is related to the host's neuraminidase while the delayed onset is more than less applicable to the metabolism of the oseltamivir phosphate, OP. Generally, Oseltamivir reduces symptomatic influenza infections such as diarrhea and cardiac events, but not influenza like illnesses [63]. Although neuraminidase inhibitors (NI) may reduce the ability of the virus to penetrate the mucus in the very early stage of the infection, their main mechanism of action is through their ability to interfere with the release and spread of progeny influenza virus from infected host cells by inhibiting neuraminidase of influenza viruses. This reduces the symptom duration by reducing the viral strain and the involvement of cytokines. These cytokines are microscopic proteins that are essential in cell signaling as they are peptides which are secreted by the cells in the immune system. The mechanism essentially slows down the viral replication; permitting the immune system to fight the virus itself.

When Oseltamivir was given to infected mice, it alleviated the symptoms of respiratory syncytial virus (RSV) that lacks neuraminidase. This phenomenon of a mechanism is inhibition of the host's endogenous neuraminidase leading to the reduction of inflammatory cytokines and GM1 ganglioside in immune cells. The mechanisms are related to symptom relief without significant viral load and is related to the inhibition of the host's endogenous neuraminidase [63]. Oseltamivir has shown promising effects geared toward the treatment of the influenza virus strains. It is a reliable NA inhibitor which blocks the function of the viral neuraminidase protein. While Oseltamivir is effective in treating the flu and its several strains, it lacks in certain aspects of treatment and may cause a

serious risk of side effects. Taking Oseltamivir can result in an increased risk of nausea, vomiting, nausea, headache and renal pain. It is also the source of major respiratory infections such as pneumonia, croup, bronchitis and some urinary tract infections. A disproportionality analysis showed that signals for vomiting and hallucinations were detected in younger patients who were given Oseltamivir. In addition, psychiatric disorders were most common in younger and older patients, while gastrointestinal disorders were most common in adult given Oseltamivir. In 2018, Influenza rates were highest in children 10 years or under. A study was carried out by the WHO, World Health Organization, further proved that children 10 years or younger were the most vulnerable to the influenza during the 2018 influenza season. It could be postulated that those children didn't produce as many immune cells as they were not exposed to the previous influenza pandemic of 2009. A strain of the virus, known as A1 (H1) pdm09 was not present in children during the 2018 pandemic, the same strain found in the 2009 Canadian influenza outbreak [64]. A similar study was done in Japan for children taking Oseltamivir. In 2007, reports of 70 deaths related to abnormal behaviors were reported in Japan, with this death being associated with children and adolescents taking Oseltamivir [57]. Nonetheless, Oseltamivir is a reliable neuraminidase inhibitor that not only blocks the viral neuraminidase protein, but also provides two vastly different mechanisms to combat this highly mutagenic virus. See Table 4 on the next page.

Table 4: Comparison table for the drugs in the treatment of influenza.

	Oseltamivir	Zanamivir	Favipiravir
Trade Name	Tamiflu	Relenza	Avigan
Prophylaxis	Adults and adolescents 13 years or older with 75mg PO once a day	Adults and pediatric patients 5 years of age and older with two 5mg PO twice a day	Adults and pediatric patients 12 years and older with 800mg taken twice daily
Dosing Regimen	Recommended dose is 75mg twice daily, one 75mg capsule or 12.5ml of oral suspension twice daily, for five days	Recommended dose is two inhalations one 5-mg blister per inhalation for a total dose of 10 mg, twice daily, 12 hours apart, for 5 days	Clinical trials are currently underway and recommending a starting dose of 1600mg twice daily, followed by 600 mg twice daily for the next 9 days
Inhibitors	Phosphate salt and an active metabolite, oseltamivir carboxylate, which is a selective inhibitor of neuraminidase enzymes	Sialic acid analogue supplied as a dry powder for oral inhalation, using the Diskhaler device	Nucleoside analog and phosphorylated by cellular enzymes into F-TRP

Administration	Oral route in the form a capsule or an oral powder for pediatric patients	To respiratory tract by oral inhalation only	Oral administration has proved to be the most significantly effective method
Adverse effects	Mostly well tolerated. Can lead to nausea, vomiting and even diarrhea	Anaphylaxis, bronchospasms, pulmonary, cardiovascular events may occur. In addition, headaches, diarrhea and nausea may occur	Mild to moderate diarrhea, asymptomatic increase of blood uric acid and transaminases and a decrease of neutrophil count
Effective concentration (EC)	0.075 Highly effective if treated within 48 hours but if administered within 12 hours of fever onset, the median illness reduced by 41%	0.033 Most effective if treated within 30 hours after an onset of symptoms and relieves symptoms after 3 days. In addition, Placebo studies have been conducted but have varied due to population related factors in different countries	Unknown Viral replication has persisted for about a week until major symptoms have dissolved. Has shown better efficacy than oseltamivir after a delayed administration. Mostly effective against a broad range of RNA viruses but ineffective against DNA viruses
Terminal half-life	8-hour half-life	2.5-hour half-life	2 to 5.5 h half-life

Zanamivir

Prior to the discovery of Oseltamivir, a company known as Australian Biotech firm Biota Holdings developed the antiviral drug known as Zanamivir. This drug was licensed by Glaxosmithkline, a pharmaceutical company, in 1990 which was later approved by the US Food and Drug Administration, FDA, in 1999 [65]. Glaxosmithkline marketed this drug under the name Relenza; becoming the first neuraminidase inhibitor to be commercially developed. It was designed as an inhalation powder for oral administration and approved for treatment of acute illnesses in adults and pediatric patients aged 7 year of age for no more than 2 days.

The mechanism of action of Zanamivir is similar and much more in simplistic version that that of Oseltamivir. The antiviral drug binds to the active site of the

neuraminidase protein; rendering the influenza virus unable to escape hosts and infect others. In other words, the mechanism is the inhibition of the influenza virus neuraminidase with a possibility of alteration of virus particle aggregation and release. It interferes with the function of the influenza neuraminidase enzyme which causes a subsequent interference with deaggregation and release of the viral progeny [66]. It is concentrated in the lungs and the oropharynx with 15% of the solution being absorbed and excreted in urine. The mechanism essentially inhibits the viral neuraminidase, similar to that of Oseltamivir. In terms of mutations, Zanamivir has only a single difference compared with the natural DNA ligand and does not need any structural change in the NA to bind. Therefore, mutations conferring resistance to Zanamivir would most likely impact on substrate binding, compromising the fitness of the NA; the more differences from the natural ligand, the more potential targets for resistance.

The anti-flu drug Zanamivir was discovered before Oseltamivir, but it has some limitations: it must be administered as a dry powder puffed into the lungs by an inhaler. People would prefer to take a pill such as Oseltamivir rather than an inhaled dry powder. Not only does the inhalation powder promote an inconvenience to its consumers, but it can also lead to drastic side effects. The glaring side effect of Zanamivir is that of Bronchospasms, which poses as a serious health risk. In turn, this can lead to allergic reactions causing anaphylaxis, oropharyngeal edema, and serious skin rashes. In addition, this drug can result in bacterial infections. While these glaring side effects may seem alarming, Zanamivir has shown several positives. Compared to Oseltamivir, which results in an increased risk of headache, nausea, and renal pain, Zanamivir showed no signs of these side effects (Table 4). In addition, Zanamivir produces no neuropsychiatric reactions such as adverse delusions, hallucination and abnormal; compared to that of Oseltamivir. Substantially, Zanamivir is not known to cause any toxic effects and has a low systemic exposure to the body and is, nonetheless, one of the most effective antiviral drugs used to treat the influenza virus.

The effect of Zanamivir can vary in children and adults. This drug is a primary risk for people with asthma and chronic pulmonary disease. If treating this drug with asthmatics, people with asthma could induce bronchospasms. As this drug produces a greater risk for bronchospasms, Oseltamivir is a better alternative as it does not require administration by means of a dry powder. Since this inhalation powder is designated for adults and pediatric patients 7 years or older, it is logical to assume that children under the age of 7 will have the most severe side effects. Hence, adults are less prone to have serious side effects than that of children. All ages can produce side effects from Zanamivir with those having preexisting health conditions such as asthma, pulmonary disease, and allergies becoming more susceptible.

Favirpavir

The Japanese approved of a new drug in 2014 that would compete with the previously introduced antiviral drugs. This drug was discovered through the screening chemical library for antiviral activity against influenza virus by Toyama Chemical Co., Ltd. The Toyama Chemical Co., desired for their new drug “Avigan” or Favipiravir to become a greater version to that of Tamiflu. In 2015, the US Food and Drug Administration approved of Favipiravir. Just recently, Sihuan began trials of Favipiravir for the infamous COVID-19 which has shown some promising signs for treatment. As of March 17, 2020,

China concluded that Favipiravir was an effective treatment against the new pandemic, COVID-19.

Favipiravir more commonly known as T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) selectively and potently inhibits the RNA-dependent RNA polymerase (RdRP) of RNA viruses. Favipiravir acts by converting itself intracellularly into its active, phosphoribosylated form, which is recognized as a substrate by the viral RNA-dependent RNA polymerase and thus favors the RNA virus over DNA virus and mammalian cells. This can also inhibit the replication of other RNA viruses which include neglected and (re)emerging viruses.

Favipiravir is effective against strains resistant to NAIs and has been widely used to treat patients infected with the Ebola virus, the Lassa virus, and COVID-19. However, there is strong evidence that favipiravir acts as a mutagen by incorporating into both positive and negative stranded RNA and being aberrantly copied as multiple bases [67]. Because of its antiviral activity against different RNA viruses and its high barrier for resistance, the potential of Favipiravir as a broad-spectrum antiviral seems promising, but safety and potency issues should be overcome before this drug or similar molecules could be used to treat large patient groups [68]. It is used in China to treat Severe Fever with Thrombocytopenia Syndrome (SFTS) where patients experience symptoms such as high fever, gastrointestinal tract symptoms, hemorrhagic tendency, and thrombocytopenia and leukopenia in the total blood cell counts [69]. Most importantly, Favipiravir has shown hope in fighting the pandemic of COVID-19. In a recent study, treatments were started to combat COVID-19 using the antiviral drug Favipiravir. After Favipiravir treatment, lung imaging improved, body temperature returned to normal for more than 3 days, and the clinical manifestation improved for patients [70]. This antiviral drug has shown adverse side effects such as abnormal liver function tests, LFT, psychiatric symptom reactions, and digestive tract reactions. The most frequently observed Favipiravir-associated adverse event was raised serum uric acid. In ordinary COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment because of its higher 7 day's clinical recovery rate and more effectively reduced incidence of fever, cough except some antiviral-associated adverse effects. Overall, Favipiravir has been shown to be well tolerated in healthy volunteers and in influenza virus-infected patients; however, caution is needed because of the teratogenic risks of this drug [68].

Conclusion

In short, the prevalence of the Common Cold, Herpes, and Influenza warrants the demand of antiviral drugs that halt the replication process in the human body. Since there are a large variety of common cold causing agents, in which HRVs make up a large majority of those infections, it is difficult to synthesize a vaccine or an antiviral drug that produces a wide-range protection. The production of anti-viral drugs against specifically HRVs must be effective across the diverse genomes, which helps to design novel molecules to target structures or functions that are conserved through the multiple strains of HRV. To date, no compound targeting the inhibition of HRVs have been approved for pharmaceutical use; however, with promising research like the discovery of a previously unknown pocket conserved within the replication of HRVs, there is hope that an effective chemical inhibiting HRVs without many adverse effects can be found. While all the drugs available to treat the

Herpes Simplex Virus can treat both HSV-1 and HSV-2, the prodrugs that have been created seem to have a greater effectiveness in their oral administration and with smaller dosages compared to the main drugs discovered. In the future, a combination of the drugs found could be tested with multiple routes of administration to determine if a longer lasting effect including stoppage of viral transmission could occur. The antiviral drugs of Oseltamivir, Zanamivir, and Favipiravir are the epitome treatment of the Influenza virus as they have proven to effectively halt replication through different mechanisms. Specifically, both Oseltamivir and Zanamivir are NA inhibitors (NAIs) preventing the release of new virions from developing on the cell surface. In addition, Favipiravir poses as an alternative drug that not only is effective against resistant strains of NAI's but also selectively and potently inhibits the RNA dependent RNA Polymerase, known as RdRP, of RNA Viruses such as COVID-19. The aforementioned pharmaceutical drugs effectively aim to interfere with the biological mechanisms of the Common Cold, Herpes and Influenza.

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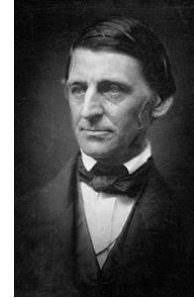


TABLE OF
CONTENTS ↑

Ralph Waldo Emerson gave a speech in 1837 that encouraged a national intellectual perspective while denouncing academic scholarship for its reliance on standard thinking. Scholars, Emmerson said, have become “indolent” and “parrot[s] of other men’s thinking.” Emerson proposed the idea that scholars think independently, and while they might rely on the work of other scholars, they produce their own work. Emerson’s speech, entitled “The American Scholar” has heavily influenced my editorship of *The Oak Leaf*.

Along with being an undergraduate research journal, *The Oak Leaf* is a teaching journal. In this issue, we have one book review and one essay by members of our faculty who are veteran teachers. One of our kinesiology professors, Melissa Parks, reviews a textbook she believes students can rely on for expert guidance should they choose to pursue a profession in health and wellness. An essay by one of our literature professors, Owen Elmore, shows students how to write an excellent critical analysis of literary art. Both scholars’ work has evidence of independent thinking, and what Emerson and his cohorts, Longfellow, and Oliver Wendell Holmes, would call a presentation of truth.

Professor Elmore’s and Professor Parks’ work tells us what teachers want to know, what they already know, and what they trust. Because this is a teaching as well as an undergraduate research journal, we can learn what our colleagues do in their disciplines.

The student essays show that students can meet the standards set by their professors. Each piece in this issue is the result of revision, of even deeper thinking, of patient guidance, and finally, of independent thought. If you are not impressed by the strength of the students’ words, be impressed by their persistence and resilience. Look at how a young woman working to become a RN recognized the similarities between people she may one day care for and characters she met in a novel. Notice that a senior student in Missouri and one in the Bahamas fell in love with a dead Native American woman writer, so much so they want to tell you about her. A freshman student from Conroe, Texas identified the history that South Americans have lived through with a story about a retired colonel. A deputy sheriff earning a degree from LSUA shares a review of literature about stalking, *stalking!* Chemistry majors remind us of the curiosity their work requires, and finally a former soldier who served in Afghanistan reviews a book that deals with what he is familiar with in his current job as a special agent.

Emerson wanted to grow “good and wise” men—this small journal shows that our campus is growing good and wise students, both men and women. Their work incorporates their knowledge of the wider world, and we are richer for it.

CONTRIBUTORS

TABLE OF
CONTENTS ↑

Jerad Daniel is a Criminal Justice student at LSUA and a deputy sheriff with over 15 years of law enforcement experience. Daniel is a two-time recipient of his agency's Uniform Patrol Deputy of the Year Award. He is POST certified and has several instructor certifications in various areas of law enforcement including standardized field sobriety testing, police motorcycle operation, and emergency vehicle operation. He teaches several courses at the regional law enforcement academy. Daniel enjoys the challenge of combining physics with law enforcement. He supports his local community and church by volunteering, and in fact, began his career in law enforcement by serving his community as a volunteer deputy. Daniel is married to his wife of ten years and is the father of two boys who are two and seven years old.

Owen Elmore, Ph.D., is a veteran English professor at LSUA and an authority on Southern Literature. He has also published several essays about the work of William Faulkner and is listed in the *Faulkner Annotated Bibliography* published by Rowan and Littlefield.

Gardenia Evans lives in Nassau, The Bahamas, with her family and pets. She began earning her bachelor's degree in English years ago. She is scheduled to complete it in December 2021. Evans discovered her passion for literature and writing in her mid-teens and is privileged to be able to continue to hone her skills. She hopes to enter graduate school and ultimately write stories of her country's cultural history. Presently employed by a quasi-governmental agency, Evans notes that her studies have proven invaluable in her research work required for preparation of socio-economic positions papers in support of the Government's mandate. In her spare time, she enjoys dancing in cultural festivals, classical singing and writing haikus.

Noah DeMoss is a senior Biochemistry major at Oklahoma Baptist University's James E. Hurley College of Science and Mathematics. After completing his undergraduate education, he plans to attend medical school. DeMoss is passionate about helping to teach science and math to high school kids. He loves to play piano and enjoys being part of the church choir.

Emma Downing is a senior at Oklahoma Baptist University who will complete a BS in Biochemistry in the spring of 2022. She has worked on several research projects, including the synthesis of different SubPc-Zn-Porphyrin conjugates for applications in artificial photosynthetic systems and other molecular electronic devices as well as tryptophan-derived treatments for Non-alcoholic Fatty Liver Disease. At the conclusion of her studies, she plans to pursue her Ph.D in Medicinal Chemistry to further expand the growing field of drug design and synthesis.

Mary Gustin is a recent graduate (B. A. English, May 2021) of Louisiana State University Alexandria. She also holds a B. A. in French and an M. A. in Teaching English as a Second

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Tia Malak is an English major from Conroe, Texas. Originally from Charleston, South Carolina, she is married, and mom to two young children.

John Marks, Ph.D., is an assistant professor of Criminal Justice at LSUA.

Grant Martin has been a resident of Tulsa, Oklahoma for the past twenty years. A senior at Oklahoma Baptist University, Martin will earn a BS degree in 2022. He plans to pursue a career in Pharmacy. Martin's diagnosis of severe food allergies inspired him to help others in his future medical profession. In his spare time, Martin likes to spend time with family, play board games, workout, and watch sports.

William Newman from San Manuel, Arizona, is an Oklahoma Baptist University senior biochemistry major and competes in college-level swimming. His excellence both in and out of the water has led William to be fascinated by the physiology of the human body. Due to this intricacy, William plans to attend medical school and pursue a career in healthcare, to better help others in their health.

Vi Nguyen is a sophomore at LSUA. She is from Maryland and decided to take a big leap and attend college out of state where she could flourish in her studies. Her interest in writing started when she was in elementary school where she would write creative skits for a school club. As she progressed as a student, she maintained an interest in writing. She would like to give a special thanks to her English professor who has made this opportunity possible and who has guided her through the entire process.

Melissa Parks, Ph.D., has several national fitness certifications, specifically with American Council on Exercise and American College of Sports Medicine. She has earned professional development hours in nutrition and fitness/sport conditioning. The certifications and additional training certify her for instructing group exercise sessions, whether with continuing education students engaging in lifelong learning or athletic squads.

Matthew Stokes, MA, has taught composition and ESL at LSUA for over six years. His master's thesis from Louisiana Tech University was about humanity's role in managing nature as seen in the works of William Faulkner, Robert Frost, and Emily Dickinson. Stokes is a native of Monroe, Louisiana who taught English in China for two years--one year in Inner Mongolia Province and one year in Xinjiang Province. He has been married to his wife, Wang Ling, for over twelve years. Together, they raise various animals, including a donkey, a horse, several sheep, several goats, two barn cats, and several dogs.

Richard Thompson will graduate from LSUA in December with a bachelor's degree in Criminal Justice. He is a Special Agent with the U.S. EPA- Criminal Investigation Division and assigned to the Southwest Area Office- Louisiana Investigations Branch. Prior to

employment with EPA-CID, Thompson was employed with the Saginaw (Michigan) Police Department, assigned to uniform road patrol, the Bay Area Narcotics Enforcement Team, the Saginaw Police Emergency Services Team (SWAT), and homicide investigations. Thompson retired from the U.S. Army Reserve after 24 years of service which included a one-year deployment to Afghanistan as a Combat Advisor to the Afghan National Army.

Lakshmi C Kasi Viswanath, Ph.D., (Oklahoma State University) formerly of Oklahoma Baptist University, is now an Associate Professor at Utah Valley University. Her research focus lies on supramolecules, development of donor acceptor conjugates for organic solar cells and light harvesting systems. She has published many articles in international journals including a book chapter. She serves as a journal reviewer and actively participates in ACS regional and national conferences.