HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on April 17, 2020 via webinar. The meeting was called to order by Dr. Messer, Chair at 9:30 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Angela Babin, RPh	Present	Rishi Sawhney, MD	Present
Jean Baemayr, PharmD- Secretary	Present	Glenn Shipley, DO	Present
John Bennett, MD	Present	Ashton Wickramasinghe, MD	Present
Bonnie Burroughs, RPh	Present		
German Corso, MD	Present	Tim Bray (non-voting)	Absent
Catherine Hall, PharmD	Present	Brad Fitzwater, MD (non-voting)	Present
Jeanna Heidel, PharmD	Present	Connie Horton, APRN (non-voting)	Absent
Dana Hopkins, RN	Absent	Raul Luna, RN (non-voting)	Absent
Jeffery Matthews, MD	Present	Mike Maples (non-voting)	Absent
Mark Messer, DO- Chair	Present	Nina Muse, MD (non-voting)	Absent
David Moron, MD	Present	Peggy Perry (non-voting)	Absent
Kenda Pittman, PharmD	Present	Rachel Samsel, (non-voting)	Absent

Guests Present: Ann Richards, PharmD, HSCS State Hospitals; Lisa Mican, PharmD, Austin State Hospital; Robert Zertuche, RN (for Connie Horton), HSCS State Supported Living Centers.

Introduction and Other Information

Dana Hopkins has been selected as the new state hospital nurse representative to the committee.

Conflict of Interest Declaration

The committee members present did not disclose any new conflicts.

Review of Minutes

On a motion by Dr. Messer, seconded by Dr. Bennett, the minutes from the October 25, 2019 and the January 31, 2020 meetings were approved as previously distributed.

Unfinished Business

TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)

The TAC with revisions as approved by the committee was forwarded to the Rules Coordination Office liaison. The draft was posted on the HHSC website for informal comment through Tuesday March 31 and no comments were received. The proposal packet is currently being prepared and is due to the Rules Office by May 12. Anticipated rule effective date is January 2021.

New Business

New Drug Applications

Conflict of Interest disclosure forms were previously received from the non-committee members who had submitted the new drug application and/or prepared the monograph. No new conflicts were disclosed.

Midazolam nasal spray (Nayzilam®)

Presented by Dr. Mican. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

On a motion by Dr. Matthews, seconded by Dr. Messer, it was recommended to add midazolam nasal spray to the formulary.

The formulary check list was completed and no issues were detected. As this product has been on the market for less than one year, system midazolam nasal spray use will be evaluated in one year to determine if any adverse drug reactions or medication errors have occurred.

Adverse Drug Reaction Reports

The committee discussed one adverse drug reaction report that was received from the field. This adverse event was reported to the FDA's MedWatch program.

ADR: olanzapine/oculogyric crisis

A 22-year-old African American male resident of a state supported living center underwent total intravenous anesthesia (TIVA) on 2/25/20. In the morning of 2/26/20 he was cleared from anesthesia. Around 1:00 p.m. 2/26/20 he was noted to have both eyes rolled upward and was unable to gaze downward for more than a few seconds. This resolved spontaneously after about 30 minutes. During this time, he remained ambulatory and oriented. He did not have nystagmus. Around 3:00 p.m. the reaction began again and stopped spontaneously after about 15 minutes. Current medications at the time of the reaction included olanzapine 20 mg orally at bedtime, benztropine 1 mg orally twice daily, cholecalciferol, divalproex sodium ER, fenofibrate, milk of magnesia, miconazole topical, salicylic acid topical soap, and

adapalene/benzoyl peroxide topical. He was treated with 50 mg diphenhydramine intramuscular (IM) once and started on diphenhydramine 50 mg orally at bedtime. Olanzapine was stopped. Medications administered during TIVA included sevoflurane, ketamine, midazolam, propofol, dexmedetomidine, rocuronium, fentanyl, dexamethasone, ketorolac, and remifentanil. These medications, including olanzapine, were run through Micromedex drug-drug interaction software. Although multiple interactions were found, none included elevated serum olanzapine levels or neurologic issues. Of note, the patient denied smoking anything other than tobacco or taking any street drugs or medications that were not his.

Hepatitis C Drug Purchases

For the second quarter of fiscal year 2020 (December 2019-February 2020), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $0

State Supported Living Centers: $0

Quarterly Non-Formulary Drug Justification Report

For the second quarter of fiscal year 2020 (December 2019-February 2020), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the second quarter of fiscal year 2020:

- Acetaminophen-caffeine- pyrilamine (Midol Menstrual Complete®)
- Deutetrabenazine (Austedo®)
- Flaxseed oil
- Sitagliptin (Januvia®)
- Clotrimazole-betamethasone dipropionate (Lotrisone®)- added at January's meeting

Esketamine nasal spray (Spravato®) system usage review

Esketamine nasal spray (Spravato®) was newly added to the formulary in April 2019. As this product had been on the market for less than one year at the time it was added to the formulary, state hospital and state supported living center esketamine nasal spray (Spravato®) usage from April 1, 2019 through March 31, 2020 was reviewed. Purchases were $20,537 for the state hospitals (one facility) and $0 for the state supported living centers. No adverse drug reactions or medication errors related to the use of esketamine nasal spray (Spravato®) were reported.

Aripiprazole lauroxil (Aristada Initio®) system usage review

Aripiprazole lauroxil (Aristada Initio®) was newly added to the formulary in April 2019. As this product had been on the market for less than one year at the time it was added to the formulary, state hospital and state supported living center aripiprazole lauroxil (Aristada Initio®) usage from April 1, 2019 through March 31, 2020 was reviewed. Purchases were $1795 (one unit) for the state hospitals and $0 for the state supported living centers. No adverse drug reactions or medication errors related to the use of aripiprazole lauroxil (Aristada Initio®) were reported.

Drug Formulary Sectional Review

In reviewing the formulary drug listings for endocrine agents, osteoporosis agents, and genitourinary agents, the committee discussed the following changes:

- Endocrine Agents: Add Osteoporosis Agents as a subcategory
- Osteoporosis Agents: Move to Endocrine agents as a new subcategory
- Genitourinary Agents:
  - Miscellaneous genitourinary agents:
    - Estradiol and estrogens, conjugated- remove from this section, both are also listed in the Endocrine Agents.
    - Terbutaline- remove from the formulary due to non-use.

On a motion by Dr. Messer, seconded by Dr. Bennett, the changes listed above were approved. The formulary will be updated.

Other Formulary Changes

The committee discussed the following changes to the formulary:

- Move sodium polystyrene sulfonate from the Miscellaneous Cardiovascular Agents section to the Antidotes section.
- Change the title of the Miscellaneous Analgesics & Antipyretics section to Miscellaneous Analgesic, Antipyretic, & Anti-Inflammatory Agents.
- Move colchicine from the Miscellaneous Endocrine Agents section to the Miscellaneous Analgesic, Antipyretic, & Anti-Inflammatory Agents section.
- Remove zaleplon from the formulary due to non-use.

On a motion by Dr. Messer, seconded by Dr. Matthews, the changes discussed above were approved. The formulary will be updated.

Review of Available Resources

The utility of this committee continuing to routinely update resources by adapting information that is readily available through on-line resources was discussed. The following documents that are currently due for review were considered:

- Cytochrome P450 Drug Metabolism Table- scheduled for annual review. This information is adapted from the Indiana University Department of Medicine

Division of Clinical Pharmacology website, which is routinely updated. https://drug-interactions.medicine.iu.edu/Home.aspx . Recommendation is to remove this document from the PEFC web page and provide a link above in a new document "Resource Links" to be posted on the formulary website.

- Antipsychotic adverse reaction table– reviewed at the January 2020 PEFC meeting and needs further revisions. Recommendation is to remove this document from the PEFC web page and add link to The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia in the "Resource Links" document.
- IV/IM Compatibility Table- last updated April 2008. Recommendation is to remove this document from the PEFC web page.
- Psychotropic medication audit criteria and guidelines documents- will continue to be reviewed and updated on a 3-year rolling schedule.

On a motion by Dr. Baemayr, seconded by Dr. Messer, the changes recommended above were approved.

Psychotropic Audit Checklist Criteria & Guidelines Review

The committee reviewed revised audit checklist–for non-benzodiazepine sedative/hypnotics (zaleplon and zolpidem) and the following recommendations were made:

- Remove zaleplon from the checklist, based on the recommendation to remove it from the formulary. Dr. Hall will prepare a monograph on eszopiclone for the committee to review at a subsequent meeting in order to determine if this medication should be added to the formulary.
- Clarify that the components of the audit checklist template will include the following three items:
  - Indication
  - Absolute Contraindications
  - Monitoring

The audit criteria and guidelines will be reviewed at a subsequent meeting.

On a motion by Dr. Baemayr, seconded by Ms. Babin, the revised audit checklist was approved as modifications as described above. The updated document will be posted to the PEFC website.

COVID-19 Pandemic

The state hospital draft clinical guidance memo for treating patients with COVID-19 was shared with the committee.

Issues from the Chief Medical Officer, State Hospitals

Dr. Muse was not available to present a report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley had no new information to report.

FDA Drug Safety Communications and Recalls

The FDA has issued the following safety communications and recalls that may impact our facilities:

Recalls

Phenytoin oral suspension: Taro Pharmaceuticals is voluntarily recalling two lots of phenytoin oral suspension. The reason for the recall is that product may not re-suspend when shaken which could result in under or overdosing. The population at risk is primarily infants and young children. In those patients, there is a reasonable probability that inaccurate dosing might result in a serious adverse effect such as intoxication or breakthrough seizures requiring medical intervention. For a small minority of patients, who might have severe or repeated breakthrough seizures, a drop in their phenytoin blood levels could result in life-threatening status epilepticus requiring immediate emergency room treatment. To date, Taro has not received any adverse event reports related to this recall.

Ranitidine: The FDA announced it is requesting manufacturers to withdraw all prescription and over-the-counter ranitidine drugs from the market immediately. This is the latest step in an ongoing investigation of N-Nitrosodimethylamine (NDMA) in ranitidine medications. FDA has determined that the impurity in some ranitidine products increases over time and when stored at higher than room temperatures may result in consumer exposure to unacceptable levels of this impurity. As a result of this immediate market withdrawal request, ranitidine products will not be available for new or existing prescriptions or OTC use in the U.S.

Safety-related Labeling Changes

Mirtazapine: Pregnancy and Lactation Labeling Rule (PLLR) conversion.

Atomoxetine: PLLR conversion and revisions to patient medication guide (underlined below).

- It is not known if STRATTERA will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- There is a pregnancy registry for females who are exposed to ADHD medications, including STRATTERA, during pregnancy. The purpose of the registry is to collect information about the health of females exposed to STRATTERA and their baby. If you or your child becomes pregnant during treatment with STRATTERA, talk to your healthcare provider about registering with the National Pregnancy Registry of ADHD Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhdmedications/.

- are breastfeeding or plan to breastfeed. It is not known if STRATTERA passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take STRATTERA.

Clozapine: 5.16 Anticholinergic Toxicity (Additions and/or revisions underlined below).
CLOZARIL has potent anticholinergic effects. Treatment with CLOZARIL can result in CNS and peripheral anticholinergic toxicity, especially at higher dosages, or in overdose situations. Use with caution in patients with a current diagnosis or prior history of constipation, urinary retention, clinically significant prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant adverse reactions. When possible, avoid concomitant use, with other anticholinergic medications because the risk for anticholinergic toxicity or severe gastrointestinal adverse reactions is increased.

MedWatch Safety Alerts

Montelukast: Strengthened Boxed Warning. Montelukast prescribing information already includes warnings about mental health side effects, including suicidal thoughts or actions; however, many health care professionals and patients/caregivers are not aware of the risk. The FDA decided a stronger warning is needed after conducting an extensive review of available information and convening a panel of outside experts, and therefore determined that a Boxed Warning was appropriate.

News Briefs

The following information was shared with the committee members:

FDA Approves Oral Pill For Migraine Headaches

Reuters (2/27, Maddipatla) reports that the FDA has “approved Biohaven Pharmaceutical Holding Co Ltd’s oral pill for relieving pain after the onset of migraine headaches, the drug developer said.” According to Reuters, “Nurtec ODT, chemically known as rimegepant, belongs to an emerging class of migraine treatments called calcitonin gene-related peptide inhibitors.”

Eli Lilly Does Not Expect Any Shortages Of Its Drugs Due To Coronavirus

Reuters (3/3, Joseph) reports Eli Lilly announced that “it does not expect the coronavirus outbreak to result in shortages for any of its treatments, including all forms of insulin.” Lilly “said it does not source active drug ingredients from China for any of its approved medicines and that its insulin manufacturing facilities in the United States and Europe have not been impacted by the outbreak.”

Analytical Laboratory Asks FDA To Request Recalls Of Metformin

Clinical Endocrinology News (3/5, Otto) reports, “Valisure, an online pharmacy and analytical laboratory based in New Haven, Conn., has asked the” FDA “to request recalls of the diabetes drug metformin from 11 companies after its own testing

found levels of the probable carcinogen N-nitrosodimethylamine (NDMA) exceeded those recognized by the agency as being safe, according to a petition filed with the" agency. According to the article, "several of the batches tested from a total of 22 companies contained more than 10 times the accepted 96-ng daily limit for NDMA set by the" FDA. The laboratory's "findings are in contrast to those from the FDA's own testing of metformin from eight companies." In those results which were "released Feb. 2, the agency found no NDMA in metformin from seven of the companies, and elevations within the safe limit in metformin from the remaining company." Therefore, the agency "did not issue a recall."

ASHP Discusses Impact Of Coronavirus On Pharmaceutical Supply Chains

CNBC (3/6) interviewed Michael Ganio of the ASHP about the potential impact of coronavirus on pharmaceutical supply chains. Ganio said the FDA has only confirmed one shortage due to coronavirus, but given the large number of pharmaceutical plants in China more are expected. Ganio also discussed how the lack of transparency about pharmaceutical supply chains makes it difficult to predict which drugs will be affected, and as a result pharmacies and hospitals are forced to prepare for potential shortages based on little information.

Olanzapine-Samidorphan Combo Not Superior To Olanzapine Alone

Healio (3/25, Gramigna) reports, "A combination of olanzapine and samidorphan" called ALKS 3831 "was not superior to olanzapine alone in the time to first event of exacerbation of disease symptoms in patients with schizophrenia and alcohol use disorder [AUD]," investigators concluded in a 234-patient, "phase 2, double-blind study of ALKS 3831." The findings were published online in the Journal of Clinical Psychiatry.

DEA Increases Production Limits For Certain Controlled Substances

Reuters (4/7, Joseph) reports the DEA announced "it was increasing production limits by 15% for certain controlled substance medicines that were in high demand due to the COVID-19 pandemic." The DEA's decision "includes painkillers, such as fentanyl, morphine and hydromorphone, and certain cough or cold-medicine ingredients like codeine, ephedrine and pseudoephedrine."

Open Forum

No items.

Next Meeting Date

The next meeting is scheduled for July 31, 2020.

Adjourn

There being no further business, the meeting was adjourned at 1:47 p.m.

Approved: ***Mark Messer***

Mark Messer, D.O., Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

- Appendix A – midazolam nasal spray (Nayzilam®) monograph

Appendix A

Midazolam (Nayzilam®) nasal spray, CIV

Classification:

Benzodiazepine

Pharmacology

Nayzilam® (midazolam) is thought to potentiate GABAergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

Indication- FDA & literature supported non-FDA

FDA Approved: Nayzilam® is FDA approved in those 12 years of age or older with epilepsy for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e. seizure clusters, repetitive seizures) distinct from a person's usual seizure pattern.

Non-FDA Approved: Midazolam intranasal is also recommended by some treatment guidelines for prolonged seizures and status epilepticus, particularly when IV access is not available and in prehospital settings.

Pharmacokinetics

Parameter	Details
Absorption	Nasal administration of 5 mg dose in adults has a mean absolute bioavailability of 44%. Median Tmax 17.3 minutes; mean Cmax 54.7 ng/mL; mean AUC 126.2 ng.hr/mL.
Distribution	97% bound to plasma protein (primarily albumin) in adults and pediatric patients. The metabolite 1-hydroxy-midazolam is 89% bound to plasma protein.
Metabolism	Primarily metabolized by liver and intestinal CYP3A4 to the active metabolite 1-hydroxy-midazolam. This active metabolite is thought to be at least as potent as the parent compound and contributes to the pharmacologic activity of midazolam.
Excretion	Principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Dosage/Administration

Nayzilam® (midazolam) is stored at controlled room temperature and administered by the nasal route only via a 5 mg per 0.1 mL single-dose nasal spray unit.

Do not open blister packaging until ready to use.

Do not test or prime before use.

The initial dose is one spray (5 mg) into one nostril.

One additional dose, one spray (5 mg) into the opposite nostril with a second nasal spray unit may be administered after 10 minutes if no response to the initial dose.

Do not use more than two doses to treat a seizure cluster. It is recommended to treat no more than one episode every three days and no more than five episodes per month.

Use in Special Population

Pregnancy

No adequate well-controlled studies in pregnant women. Available data suggest the class of benzodiazepine is not associated with marked increases in risk for congenital anomalies. Some early studies with considerable limitation suggested a relationship between benzodiazepines and congenital anomalies such as cleft lip and/or palate. More recent studies have not found these risks. Reduced fetal movement, fetal heart rate variability, floppy infant syndrome, dependence and withdrawal are clinical considerations during second and third trimester exposure during pregnancy or immediately prior to or during childbirth. Clinical manifestations of withdrawal may include hypertonia, hyperreflexia, hypoventilation, irritability, tremors, diarrhea and vomiting. These complications can appear shortly after delivery to 3 weeks after birth and can persist for hours or several months. Nayzilam® (midazolam) should be used during pregnancy only if the potential benefit to the mother justified the potential risk to the fetus. Advise pregnant women and women of childbearing age of the potential risk to the fetus.

Lactation

Midazolam is excreted in human milk. Studies regarding the effect of midazolam in breastfed infants or on mild production have not been performed. Post marketing reports of lethargy, somnolence and poor sucking has been reported. Potential risk to breastfed infants should be considered along with mother's clinical need for the medication.

Pediatric Use

Safety and effectiveness of Nayzilam® (midazolam) in pediatric patients below the age of 12 years have not been established.

Geriatric Use

Studies utilizing Nayzilam® (midazolam) in patients 65 years and older were not sufficient in numbers of subjects to determine if they respond differently than younger adults. Geriatric patients may have prolonged exposure (AUC increased 21%) to midazolam due to longer elimination half-life of midazolam and its

metabolites (terminal half-life increased approximately 2 hours) and those over 70 years of age may be particularly sensitive. Increased risk may be observed in those concomitantly prescribed other CNS depressants, particularly narcotics. If administered to geriatric patients close monitoring is recommended.

Renal Impairment

Trials did not include adequate numbers of subjects with moderate to severe renal impairment to establish safety and efficacy. Those with moderate to severe renal impairment may have a longer elimination half-life of midazolam and its metabolites, which may result in prolonged drug exposure. Studies in those with mild renal impairment showed similar pharmacokinetics compared to those without renal impairment for midazolam and its metabolites.

Congestive Heart Failure

Those with congestive heart failure may have prolonged drug exposure due to slower elimination of the medication (2-fold increase in elimination half-life and 25% decrease in plasma clearance).

Contraindications

Hypersensitivity to midazolam

Acute narrow-angle glaucoma

Precautions

Boxed Warning: Risk from concomitant use with opioids may increase the risk for profound sedation, respiratory depression, coma and death. Reserve prescribing of benzodiazepines with opioids for those whom alternative treatments are inadequate. If coprescribed, use lowest effective dose and monitor closely for respiratory depression and excessive sedation.

Risk of cardiorespiratory adverse reactions are greater risk in geriatric patients and those with chronic disease states or decreased pulmonary reserve such as COPD. Hypotension may also occur, and risk may be greater in those coprescribed narcotics.

Central nervous system depression from concomitant use with other central nervous system depressants such as barbiturates, alcohol or other CNS depressants such as opioids may occur and may increase the risk for hypoventilation, airway obstruction, desaturation or apnea.

Concomitant use with moderate or strong CYP 3A4 Inhibitors (see interactions) may increase the risk for CNS depression due to higher midazolam exposure.

Suicidal behavior and ideation may be increased with antiepileptic medication including midazolam. Those prescribed anticonvulsants should be monitored

for the emergence of worsening depression, suicidal thoughts or behavior and/or any unusual changes in mood or behavior. Onset may be observed as early as 1 week after starting anticonvulsant treatment in a pooled analysis. The observed relative risk (incidence of drug event with AED/incidence with placebo) was higher in clinical trials for epilepsy (RR 3.5) than clinical trials for psychiatric (RR 1.5) or other conditions (RR 1.9), but the absolute risk differences were similar for epilepsy and psychiatric indications.

Impaired cognitive function including impairment of recall for several hours following a dose. Motor vehicles and hazardous machinery should not be operated until the effects of the medication have subsided. Care should be taken to ensure safe ambulation.

Glaucoma exacerbation may occur as benzodiazepines may increase intraocular pressure. Midazolam may be used in those with open-angle glaucoma if they are receiving appropriate therapy. Use in narrow-angle glaucoma is contraindicated.

Nayzilam® (midazolam) is a controlled substance and may have risk for abuse and dependence.

Adverse Effects

Adverse reactions occurring in 2% or more of Nayzilam® (midazolam) treated patients and at a rate greater than placebo after two 5 mg intranasal doses (administered between 10 minutes and 6 hours following the initial dose) were:

- Nasal discomfort (16%)
- Somnolence (9%)
- Throat irritation (7%)
- Rhinorrhea (5%)
- Headache (2%)
- Dysarthria (2%)
- Increased lacrimation (2%)
- Abnormal product taste (4%) also reported in the Nayzilam® (midazolam) 5 mg single intranasal dose group.

In a phase 1 study with 292 adult and adolescent patients with epilepsy, two patients (one with a history of sleep apnea) experienced a decrease in peripheral oxygen saturation and required therapeutic supplemental oxygen.

Monitoring

- Monitor for any signs or symptoms of cardiorespiratory depression after administration.

- Monitor for resolution of seizure activity.

Interactions

- **Moderate (e.g. erythromycin, diltiazem, verapamil) or strong (ketoconazole, itraconazole, clarithromycin) CYP3A4 Inhibitors:** Avoid coadministration with moderate to strong CYP3A4 inhibitors and use caution with mild CYP3A4 inhibitors. Concomitant use may reduce clearance and result in prolonged sedation.
- **Strong CYP3A4 inducers (e.g. phenytoin, phenobarbital, primidone, carbamazepine):** Concomitant use may decrease exposure to Nayzilam® (midazolam) 16-26%
- **Moderate CYP3A4 inducers (e.g. clobazam, eslicarbazepine, felbamate, oxcarbazepine, rufinamide, topiramate):** Concomitant use may decrease exposure to Nayzilam® (midazolam) 8-15%
- **Opioids (e.g. morphine, hydrocodone, oxymorphone, codeine, fentanyl):** Increased risk for respiratory depression.
- **CNS depressants (e.g. other benzodiazepines, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, opioids, alcohol):** Increased risk of hypoventilation, airway obstruction, desaturation, or apnea.

Efficacy

Effectiveness of Nayzilam® (midazolam) nasal spray was established in a randomized, double-blind, placebo-controlled trial (NCT 01390220) in subjects 12 years of age or older. Tolerability was initially assessed in a test-dose phase in 292 subjects, who in the absence of a seizure received two 5 mg Nayzilam® (midazolam) nasal doses separated by 10 minutes. Patients were excluded if they failed to meet pre-defined blood pressure, heart rate, sedation, EKG and peripheral oxygen saturation criteria. In the comparative phase, 201 subjects treated a single seizure cluster episode in an outpatient setting with either a blinded dose of Nayzilam® 5 mg (134 subjects) or placebo (67 subjects). If the seizure activity persisted or recurred, patients in both groups had the option to receive a subsequent unblinded dose of Nayzilam® 5 mg to be used between 10 minute and 6 hours after administration of the initial blinded dose of study drug.

The primary endpoint was termination of the seizures within 10 minutes after the dose and absence of a recurrent seizure within 6 hours after the dose. Termination of seizure occurred within 10 minutes after the dose in 80.6% Nayzilam® group and 70.1% placebo group. Absence of seizure recurrence between 10 minutes and 6 hours after the initial dose was 58.2% for Nayzilam® and 37.3% for placebo. Those treated with Nayzilam® also experienced a statistically longer time to next seizure than the placebo group.

Summary of Notable Treatment Guidelines

Guidelines are consistent in offering supportive measures during prolonged seizures or status epilepticus and include monitoring airway, breathing and circulation vitals, blood glucose, oxygenation.

- Neurocritical Care Society Treatment Guidelines
  - Benzodiazepines recommended as emergent initial therapy.
  - IV Lorazepam noted to be the drug of choice (strong recommendation, moderate quality).
  - Midazolam is the drug of choice for IM administration (strong recommendation, moderate quality). Rectal diazepam can be given when there is no IV access and IM administration of midazolam is contraindicated (strong recommendation, moderate quality).
- Scottish Intercollegiate Guideline Network- Adult guideline 2015 available at http://www.sign.ac.uk
  - Immediate measures- Once five minutes of seizure activity have passed, treatment should be given as quickly as possible. Initial management of prolonged seizures should be with benzodiazepines.
  - Patients with prolonged tonic-clonic seizures that have lasted five minutes or more should be given: midazolam 10 mg buccally or intranasally, or lorazepam 4 mg IV if midazolam is unavailable, or diazepam 10 mg IV or rectally if midazolam and lorazepam are unavailable
- American Epilepsy Society
  - The initial therapy phase should begin when the seizure duration reaches 5 minutes and should conclude by the 20-minute mark when response (or lack of response) to initial therapy should be apparent.
  - A benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability (level A evidence, four class I RCTs).
  - For prehospital settings or where the three first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives (level B evidence).

Caregiver and Patient Preference

One study surveyed caregivers of children with epilepsy regarding information on the comfort, efficacy, ease of use, and time of administration for patients receiving both abortive seizure medications. Subjects were patients with epilepsy prescribed intranasal midazolam and/or per rectum diazepam. A total of 153 responses were evaluated. Of those responses, 59 respondents reported administering both medications. Among parents who expressed a preference for one medication over the other, significantly more parents felt overall greater comfort with intranasal

midazolam compared with rectal diazepam, intranasal midazolam was perceived as easier to use and more effective (87%, $p < 0.0001$) than rectal diazepam.

Systematic Review and Meta-Analysis

Randomized controlled trials comparing non-IV midazolam with diazepam (by any route) in patients of all ages with early status epilepticus defined either as seizures lasting >5 min or as seizures at arrival in the emergency department were evaluated. Clinical seizure cessation within 15 min of drug administration and time from arrival in the emergency department to seizure cessation as well as other outcomes were assessed. Nineteen studies were included in the analysis with 1933 seizures in 1602 patients, of these, 1573 were less than 16 years of age. For seizure cessation, non-IV midazolam was as effective as diazepam via any route (RR: 1.03; 95% CIs: 0.98 to 1.08). Time interval between arrival and seizure cessation was significantly shorter with non-IV midazolam than with diazepam by any route (mean difference: -3.67 min) and a similar result was found for time from arrival to drug administration (mean difference: -3.56 min). A minimal difference was found for time interval from drug administration to clinical seizure cessation, which was shorter for diazepam by any route than for non-IV midazolam by any route (mean difference: 0.56 min); however, not all studies reported information on time intervals. Only one study was entirely conducted in an adult population (21 patients, aged 31 to 69 years) and showed no difference in efficacy or time to seizure cessation after drug administration between intranasal midazolam and rectal diazepam.

Dosage Forms

- Each single-dose nasal spray unit delivers 5 mg of midazolam in 0.1 ML of solution
- Nayzilam® (midazolam) nasal spray available in twin pack
- Diastat® (diazepam) rectal gel 10 mg, 20 mg available in twin pack
- Diastat® (diazepam) rectal gel **pediatric** 2.5 mg available in twin pack

Special Considerations

Nayzilam® (midazolam) nasal spray has a medication guide associated with this product.

Diastat® (diazepam) rectal gel is dispensed locked to deliver a particular dose. Since diazepam rectal gel is weight based this results in 5 diazepam rectal gel syringes needed as stat floor stock per treatment area deliver a particular needed dose in an emergent situation. Since Nayzilam® (midazolam) nasal spray is a standard 5 mg dose for those 12 years of age and older and is not weight based, this would reduce the number of units of product needed as stat floor stock per treatment area and could ultimately reduce cost due to expiring unused emergency floor stock product.

Summary/Conclusion

The addition of Nayzilam® (midazolam) nasal spray to the formulary is recommended for acute emergency treatment of repetitive seizures, seizure clusters or prolonged seizures and is supported by clinical evidence and treatment guidelines. The other formulary product available for prehospital settings or other settings where IV access is not available is diazepam rectal gel. The midazolam nasal spray option may provide a more desirable route of administration during seizure activity.

Recommendation

Addition of Nayzilam® (midazolam) nasal spray to the formulary is recommended.

References

- Product Information: Nayzilam® (midazolam) nasal spray. Proximagen LLC (per FDA), Plymouth, MN, 2019.
- Neurocritical Care Society Treatment Guideline. Neurocrit Care 2012; 17(1):3-23.
- Scottish Intercollegiate Guideline Network- Adult guideline 2015. Accessed 2/26/20. Available at www.sign.ac.uk.
- American Epilepsy Society. Epilepsy Currents 2016; 16(1):48-61.
- Nunley S, Glynn P, Rust S, Vidaurre J, Albert DVF, Patel AD. A hospital-based study on caregiver preferences on acute seizure rescue medications in pediatric patients with epilepsy: Intranasal midazolam versus rectal diazepam. Epilepsy Behav 2019. Mar;92:53-56.
- Brigo F, Nardone R, Tezzon F, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: A systematic review with meta-analysis. Epilepsy Behav 2015. Aug;49:325-36.

Lisa M. Mican, Pharm.D., BCPP

Director of Pharmacy

Clinical Pharmacist

Austin State Hospital

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