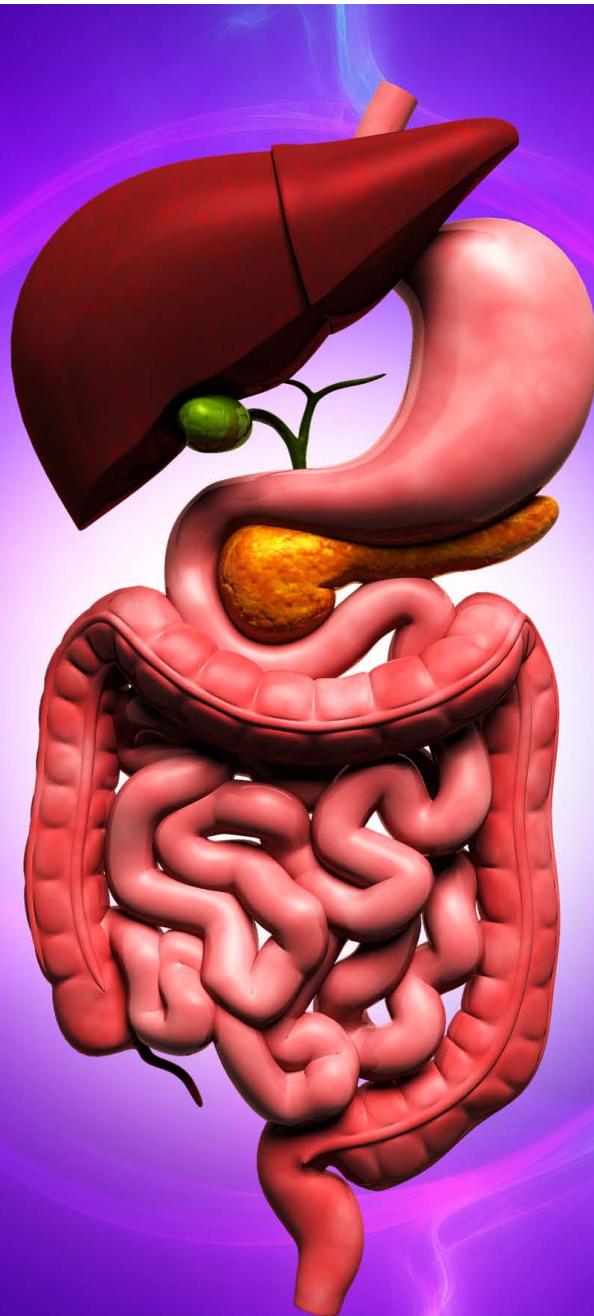


# *The New Jersey* **JOURNAL of Pharmacy**

New Jersey Pharmacists Association

Fall 2015 • Volume LXXXIX • Number 4

**RETAIL • COMMUNITY • COMPOUNDING • HEALTH SYSTEM  
DISASTER MANAGEMENT • CONSULTANT • INDUSTRY • ACADEMIA  
PHARMACY TECHNICIANS**



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## Peer Reviewed

145<sup>th</sup> Annual Meeting and Convention  
October 16, 2015 – October 18, 2015

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## **FINDING BALANCE**

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The New Jersey Journal of Pharmacy (ISSN0028-5773 USPS #380-360) is published seasonally by the NJ Pharmacists Association 782 Alexander Road, PO Box 1 Princeton, NJ 08543-0001 609-275-4246 Fax 609-275-4066 [www.njpharmacists.org](http://www.njpharmacists.org)

Periodicals Postage Paid at Princeton, NJ and additional mailing offices. Subscriptions paid for through allocation of membership dues. US Subscription \$50 per year; Foreign Rate \$100 per year.

POSTMASTER: Send address changes to The New Jersey Journal of Pharmacy, 760 Alexander Rd., PO Box 1, Princeton, NJ 08543-0001. 609-275-4246. [www.njpharma.org](http://www.njpharma.org)

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### Mission Statement:

*To advance the profession of pharmacy, enabling our members to provide optimal care to those they serve.*

## **President's Letter**

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### **FINDING BALANCE...Past, Present, Future**

Thank you for attending the 145th NJPhA annual convention October 16-18, 2015 at Harrah's in Atlantic City! This was an exciting time as we honored NJPhA past presidents, how they shaped our profession, where we stand today and how we move forward.

It was great seeing you all and having fun 'under the boardwalk.' The gift baskets were a big hit and really helped fund our Political Action Committee (PAC).

A big shout out goes to Fiona Romaine, Lisa Sarachman, Elise Barry, line officers, the convention committee and YOU who helped make this a great event!

My vision as we move forward is to continue focus on legislative issues, such as obtaining provider status. Would you consider getting more involved in this area? Your voice matters and you can make a difference when joining PAC or even visiting Capitol Hill with us. Each year, NJPhA representatives make a run to Capitol Hill to meet with state representatives, bringing issues to the table that will make a positive impact on the future of pharmacy. Hill visits are planned around May each year. Also, consider joining us in Trenton one day as we lobby for better causes.

In addition, revitalizing and strengthening the association is always a forefront in my mind. Last year's major focus on membership recruitment & retention; developing student practitioner, new practitioner and social committees; and working closely with pharmacy schools and our regional presidents will continue to be a focus.

Communication is key to our members! We have been diligently working in this area to get up-to-date information to you on the website, sending concise email communications and program announcements, and using social media. We've also updated our member records and encourage you to update us with changes in contact information.

I look forward to working with you and always welcome your input in the quest to find balance.

Professionally yours,  
Ruth Marietta, RPH, CCP  
NJPhA President 2015-2016

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### ***Message from the CEO***

#### **Is your profession one of your priorities?**

The NJPhA communications throughout the summer and fall emphasized the Finding Balance theme of the 145th annual convention this fall. The theme was fitting an anniversary year when we recognized our past presidents for their contributions to NJPhA, and linked past with present, or personal with professional. It, however, has many different meanings, and at NJPhA, it also means balancing the yearlong work and accomplishments of our outgoing committees with the goals of the incoming committees.

We recognize that committee members often balance conflicting priorities to make extra time to take on the work of the association. These committed volunteers tackle many tasks, and their time and expertise is a valuable asset that benefits our members. By definition, a committee performs a service or function, and in our case, committees undertake projects and complete tasks

that extend the reach of our small staff. The 2015 and 2016 committee volunteers have our sincere thanks for their service!

Consider offering your special area of expertise to your fellow pharmacists through volunteer service. The office can match a task with your passion and your availability. Call any time!

The message for our fall 2016 convention is Keeping the Beat for New Jersey Pharmacy Since 1870, and as an association, we will continue to perform through the professional challenges pharmacy faces.

We look forward to providing you with meeting details over the next few months.

Elise M. Barry, MS, CFRE  
NJPhA Chief Executive Officer

## ***Message from the BOT Chairman***

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Dear NJPhA Members,

This time last year, I was beginning my Presidency and it seems like yesterday! Today, I'm writing as the Chair of the Board and glad to welcome you all to this issue of the NJPhA Journal. If you were not able to make it to convention this year, we missed you in Atlantic City! It was a fun-filled weekend of innovative programming, socializing (Go Mets!) and networking. I had a great time hanging with everyone, especially our students, at our Boardwalk Bash! The CEO and office staff have made great strides and it was evident at this year's event...thank you to everyone who made it such a huge success!

I look forward to more fun in the year to come...March Madness is just around the corner and don't forget, the 2016 Convention is back at Harrah's Atlantic City in the newly-updated Convention Center, which proved to be an exciting new venue this year! You might also consider joining us in a new way... becoming more active through committees, regional leadership, or state roles is tremendously rewarding. Speaking from experience, you will be glad you did!

Warm Regards,  
Moriah Weissman, PharmD, CCP

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## ***From The Editor's Desk...***

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Dear Colleagues,

It was a pleasure to meet many of you at the NJPhA convention, I had a great time! The *NJ Journal of Pharmacy*, the official peer-reviewed journal of the NJ Pharmacists Association, is pleased to provide an issue dedicated to different aspects of gastrointestinal maladies. This issue will present highlights from the NJPhA Annual Meeting and Convention that was held in Atlantic City, NJ, October 16 -18, 2015. The articles include information concerning pediatric anorexia, appetite stimulation in the cancer patient, proton pump inhibitors and their cardiovascular warning, and irritable bowel syndrome. Our community pharmacy spotlight is dedicated to Stephen Brickman and his involvement as a pharmacist in disaster management!

The theme of the next issue is women's and men's health. Please consider becoming active in the development of the *NJ Journal*

*of Pharmacy*, through either becoming a journal committee member, submitting of an article, or being a peer-reviewer. If interested please reach out to me, Marcella R. Brown, Elise Barry, or one of the NJPhA officers. You may email ideas and submissions to marcella.r.brown@gmail.com. We can help you with a topic consideration for the journal.

With regards!

Marcella R Brown, BS, MS, PharmD, MPH, CGP, BCACP  
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Clinical Pharmacist, Enclara Pharmacia  
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# Cardiovascular Safety Warning For Proton Pump Inhibitors

By: Ana Marija Djordjevic, Pharm. D. Candidate 2016,  
Gerard Quinn , Pharm. D. Candidate 2016, Michele Pisano, PharmD, CGP

An estimated 113 million prescriptions for proton pump inhibitors (PPIs) have been dispensed annually, making this class of drugs one of the highest sellers in the United States<sup>1</sup>. Proton pump inhibitors suppress gastric acid secretion by targeting and irreversibly inhibiting the H+/K+ ATPase enzyme (proton pump) at the secretory surface of gastric parietal cells. Indications for the use of PPIs are the treatment of gastroesophageal reflux disease (GERD), gastric ulcers, erosive esophagitis, and their use as a component in Triple Therapy (ie, Prilosec® [omeprazole] amoxicillin and clarithromycin) for duodenal ulcers caused by *H. pylori*<sup>2</sup>. The recommended duration of use for nearly all indications is a maximum of 8 weeks<sup>3,4</sup>.

Though many PPIs have been made available over-the-counter (OTC), findings from recent studies have reported a possible increased risk of cardiovascular events. It has been postulated that PPIs reduce the efficacy of clopidogrel, an antiplatelet agent that has become standard in post-myocardial infarction treatment regimens which places this subset of patients particularly at risk<sup>(3)</sup>. Clopidogrel and PPIs are both metabolized by the CYP2C19 enzyme<sup>(4,5)</sup>. It has proposed that when both drugs are taken together there is a competitive inhibition. Clopidogrel requires metabolism by CYP2C19 to an active metabolite<sup>(5)</sup>.

Shah et al. sought to evaluate the cardiovascular risk of PPIs outside of a high-risk cohort. Two data sources and one prospective source were utilized to examine and conduct a data mining analysis<sup>6</sup>. Researchers utilized Stanford University's STRIDE database, which contained the deidentified encounters, diagnostic tests, ICD-9 codes and notes of 1.8 million patients. The second data source included the Practice Fusion, Inc (PF) Electronic Health Record (EHR) system and utilized the deidentified data of 1.1 million patients. Finally, the association of PPI use with subsequent cardiovascular mortality was prospectively evaluated using the data from the Genetic Determinants of Peripheral Arterial Disease study (GenePAD)<sup>7</sup>. The patients used in this cohort study underwent "elective, non-emergent coronary angiograms for angina, shortness of breath or an abnormal stress test" and cardiovascular disease was confirmed through medical records<sup>(7)</sup>.

The investigators screened the STRIDE and PF databases to determine whether the exposure to PPIs is associated with an elevated risk of myocardial infarction (heart attack) in the general population. Commercial and generic names of six PPIs were extracted. The baseline of the population was identified using the term "GERD" and used codes used to identify diseases such as the International Classification of Diseases, Ninth Revision (ICD-9) codes and Unified Medical Language System (UMLS) code. One ICD-9 code and 19 UMLS codes were used to identify the main outcome, myocardial infarction (MI). Each patient was counted according to the chronological order by which the PPI and GERD was mentioned. Two study groups were defined within

the GERD baseline. The primary study group included patients taking PPIs, which included a sub-group of patients who were not on clopidogrel therapy and the comparative control population of patients who were taking it. Survival analysis was performed using Cox proportional hazard models.

The study results incorporate clopidogrel use into the data in order to determine whether the cardiovascular complications are independent of the well documented interaction between PPIs and clopidogrel. PPIs were also compared to histamine-2 receptor antagonists (H<sub>2</sub>-Blockers), another class of medication used to treat similar disease states, in order to demonstrate that the risk of MI is independent of class and action site of the drugs.

The statistically significant adjusted odds ratio (AOR) of 1.16 (95% CI 1.09 -1.24, p-value < 0.01) indicates that PPIs as a class are associated with an increase in MI occurrence; the authors used a p-value of less than 0.01 as a cutoff reference for all of their endpoints<sup>(7)</sup>. Conversely, the adjusted odds ratio of 0.93 (95% CI, 0.86 – 1.02) indicates a lack of positive correlation between MI and H<sub>2</sub>-Blockers. The PPIs that seem to carry the least cardiovascular risk are esomeprazole (odds ratio [OR] 1.08, [95% CI, 0.88 – 1.31]) and rabeprazole ([OR] 1.12 [95% CI, 0.88 – 1.41])<sup>(7)</sup>. Clopidogrel use was found to be independent of the PPI cardiovascular warning endpoint with an AOR of 1.14 (95% CI 1.06–1.24, p-value < 0.01)<sup>(7)</sup>.

A separate survival analysis outside the author's data-mining was conducted that consisted of over 8 years of PPI use. This data shows that PPI use contributes to cardiovascular mortality, with an unadjusted hazard ratio (HR) that was calculated from the Kaplan-Meier curves of 2.22 (95% CI, 1.19 – 4.16) and an adjusted HR of 2.00 (95% CI, 1.07 – 3.78), showing the positive correlation for cardiovascular risk<sup>(7)</sup>.

Data shows that PPIs are associated with an elevated risk for MI while class wide H<sub>2</sub>-Blockers do not possess this elevated risk. These findings become potentially more dangerous as the associations found do not correlate with age, putting any users at risk of cardiovascular events. An FDA warning was issued in 2009 about PPIs and clopidogrel metabolism, which applied to high risk individuals rather than someone without heart disease who uses PPIs<sup>8</sup>. The proposed mechanism for cardiovascular adverse events recorded is inhibiting the Dimethylarginase (DDAH) enzyme, which then metabolizes asymmetric dimethylarginine (ADMA), a competitor of nitric oxide synthase (NOS). Lower NOS levels lead to less nitric oxide production causing the blood vessels to become less elastic and increases the workload on the heart<sup>(7)</sup>.

Patients involved in this study have multiple additional conditions, which may confound results. Obesity, insulin therapy, and OTC PPI use were excluded factors from the study. Misdiagnosis

and even the problem of a false positive result exist due to the limitations of data mining. The writers conclude that their report is a hypothesis and not meant to be taken as an absolute risk but rather a cautionary statement for more pharmacovigilance<sup>(7)</sup>.

Further investigation using randomized, double-blinded models should be performed to validate this study's results given its level of evidence. Nevertheless, the findings from the analysis performed in this study create a concern in PPI prescribing patterns in patients with a history of cardiovascular disease. Practitioners should consider the possible risks of further cardiovascular events in high-risk patients before prescribing PPIs and perhaps prescribe H2-blockers if found appropriate for patients. Pharmacists can make suggestions for alternative GERD therapies such as H2-blockers or antacids when amendable to such therapy. Additionally, pharmacists may also recommend discontinuation of PPI therapy if a patient has been on the PPI for longer than eight weeks and asymptomatic.

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We are grateful to the experts that review the submissions, for their recommendations greatly contribute to the quality of The New Jersey Journal of Pharmacy.

The Journal wishes to acknowledge the following clinicians who have participated in peer review:

Joanne Angilot, PharmD  
Marlene Battle, PharmD, MS, BS  
Brian J. Catton, PharmD  
Juliet Cobb, PharmD  
Janine Douglas, PharmD, BCPS  
Blessing Etuk, PharmD

Connie Garcia, PharmD, MS  
Brittany Harris, PharmD  
Sasha Libman, PharmD  
Christine Martinez, BS, PharmD  
Basirat Shoberu, PharmD  
Ealia Washington, PharmD, CGP, BCACP

# Use of Appetite Stimulants in Cancer Patients: A Review of the Literature

By: Christan M. Thomas, PharmD, BCOP and Peter Campbell, PharmD

## Introduction

Due to nausea, chemotherapy-induced changes, and other factors, cancer patients often experience decreased appetite and potentially significant weight loss. These factors—which may appear together or exist separately—are collectively known as anorexia-cachexia syndrome.

Anorexia is described as the loss of the desire to eat; cachexia is characterized by significant loss of both adipose tissue and skeletal muscle mass.<sup>1-3</sup> Taken together, anorexia-cachexia syndrome has been roughly defined as a loss of weight, muscle atrophy, fatigue, weakness, and significant loss of appetite in someone who is not actively trying to lose weight.<sup>1-3</sup> This common clinical problem occurs in up to an estimated 50% of cancer patients, as well as up to 80% of patients with upper gastrointestinal cancers.<sup>1</sup> This syndrome can affect both the quality of life for cancer patients, as well as impact overall survival.<sup>4</sup>

Consequently, clinicians seek ways to increase patients' appetite and improve outcomes in any way possible. In addition to oral nutritional supplements, appetite stimulants such as megestrol and dronabinol, as well as steroids or mirtazapine are often added to therapy.

## Megestrol

Megestrol acetate is a synthetic progestin that is approved by the Food and Drug Administration (FDA) for use in anorexia or cachexia in acquired immune deficiency syndrome (AIDS).<sup>5</sup> The exact mechanism through which megestrol acetate stimulates appetite is unknown, although it is hypothesized that this effect is due to the inhibition of catabolic cytokines such as tumor necrosis factor.<sup>6</sup> Megestrol acetate doses range from 160 to 800 mg when used for cancer-associated anorexia-cachexia, although no optimal dose has been identified.<sup>7</sup> Common adverse reactions include gastrointestinal side effects and clots.<sup>7</sup> The use of megestrol acetate has been studied in several trials with comparator arms including both placebo and active control agents.

Feliu and colleagues investigated the use of megestrol acetate in cancer patients in a placebo-controlled, double-blind trial of 150 patients with nonhormone-dependent tumors.<sup>8</sup> Megestrol acetate was administered at a dose of 240 mg/day for at least 2 months, with the comparator arm receiving placebo for the same duration.<sup>8</sup> Subjective sense of appetite (SSA) was analyzed using an analogic linear visual scale of 1 to 10. There was no significant difference in weight gain between the two groups, but there was a reported difference in the SSA between the megestrol acetate and placebo groups (p value not reported).<sup>8</sup> In a dose comparison study, Schmoll et al. randomized patients to receive megestrol acetate 480 mg/day or 960 mg/day for an 8-week study period. In the two treatment arms, patients gained a median of 3 kg and 4 kg respectively (P=not significant).<sup>9</sup> Appetite was also reported to have improved in both

treatment arms, although there was no statistically significant difference between the two doses administered.<sup>9</sup>

In a second dose comparison study, 4 doses of megestrol acetate and placebo were evaluated for the treatment of cancer-related anorexia and/or cachexia. Loprinzi et al. randomized patients to receive 160 mg/day, 480 mg/day, 800 mg/day, or 1280 mg/day of megestrol acetate, or placebo, and used physical examinations and patient questionnaires to assess weight gain and appetite stimulation.<sup>10</sup> An improvement in appetite was reported in all megestrol acetate dosage arms, with the greatest effect being seen in the megestrol acetate 800 mg/day group (p=0.02).<sup>10</sup> While there was not a statistically significant increase in weight across the various megestrol acetate dosage arms, the authors reported a positive dose response for appetite stimulation.<sup>10</sup>

Megestrol acetate has been compared to other agents used for the treatment of cancer-related anorexia-cachexia. In a placebo-controlled, double-blind trial, Loprinzi et al randomized patients to receive dexamethasone 0.75 mg four times daily, megestrol acetate 800 mg/day, or fluoxymesterone 10 mg twice daily.<sup>11</sup> Patient weights were recorded at baseline and during monthly examinations, and self-administered questionnaires were used to assess appetite at baseline and monthly during the study period. Both megestrol acetate and dexamethasone increased appetite to a greater degree than fluoxymesterone (p=0.005), while megestrol acetate and dexamethasone had similar effects in stimulating appetite (p=0.7).<sup>11</sup> In a study comparing megestrol acetate to dronabinol for the treatment of cancer-associated anorexia, Jatoi and colleagues randomized patients to receive megestrol acetate 800 mg/day plus placebo, dronabinol 2.5 mg twice daily plus placebo, or both active agents.<sup>12</sup> A significantly greater percentage of megestrol acetate-treated patients had improvement in appetite compared with dronabinol-treated patients (75% vs. 49%, p=0.0001).<sup>12</sup> Combination therapy with megestrol acetate and dronabinol was not associated with a significant appetite increase as compared to megestrol acetate alone.<sup>12</sup>

## Dronabinol

Dronabinol is a cannabinoid (synthetic delta-9-tetrahydrocannabinol [delta-9-THC]) that is approved by the FDA as an antiemetic and appetite stimulant in AIDS patients.<sup>13</sup> It works by activating cannabinoid receptors CB<sub>1</sub> and CB<sub>2</sub>.<sup>13</sup> Central cannabinoid receptors CB<sub>1</sub> are considered responsible for the appetite stimulating properties.<sup>13</sup> Doses generally start at 2.5-5 mg BID (before lunch and dinner) with a maximum dose of 20 mg/day.<sup>13</sup> Doses may be titrated based on tolerability. Adverse effects may include central nervous system depression, euphoria, abnormal thinking, and paranoia.<sup>13</sup> In addition, dronabinol may cause hypotension, hypertension, syncope, or tachycardia. Caution is suggested in patients with cardiac disorders.<sup>13</sup>

In the limited studies of dronabinol as an appetite stimulant for cancer patients, responses were variable. As mentioned previously, dronabinol 2.5 mg daily was compared to megestrol with megestrol producing a statistically significantly better improvement in appetite.<sup>12</sup> Prior to the megestrol trial, Nelson and colleagues published a phase II trial of dronabinol in 19 patients with various malignancies.<sup>14</sup> Patients received delta-9-THC 2.5 mg PO TID one hour after meals for four weeks. Eighteen patients were evaluable at study completion.<sup>14</sup> Of these, 10 completed the full course of therapy.<sup>14</sup> Thirteen of 18 patients self-reported an improvement in appetite after treatment. Six patients were assessed for weight gain.<sup>14</sup> Three patients gained weight, two maintained a stable weight, and one lost weight. Median weight gain was 1.3 kg. Reported side effects included nausea, slurred speech, drowsiness, dizziness, and “high.”<sup>14</sup>

Another study examined delta-9-THC as a way of improving taste and smell (chemosensory) perception, appetite, caloric intake, and quality of life (QOL) for cancer patients with chemosensory alterations.<sup>15</sup> This study—published in the *Annals of Oncology* in 2010—included 24 patients who were randomized to receive either dronabinol 2.5 mg or placebo by mouth twice daily for 18 days.<sup>15</sup> Twenty-one patients completed the trial.<sup>15</sup> Patients treated with dronabinol had improved chemosensory perception compared to placebo. In addition, pre-meal appetite ( $P = 0.05$ ) and proportion of calories consumed as protein increased compared with placebo ( $P = 0.008$ ).<sup>15</sup> Seven patients (64%) in the dronabinol group reported increased appetite, 3 patients (27%) had no change in appetite, and 1 patient (9%) had incomplete data. The authors did not report statistically significant differences in side effect profiles between the two groups and noted that the dronabinol was “well tolerated.”<sup>15</sup>

While not extensively studied in cancer patients as an appetite stimulant, it is important to note that dronabinol is approved by the FDA for prevention of chemotherapy-induced nausea and vomiting.<sup>13</sup> This agent may be an option for patients who require both appetite stimulation and emetic control.

### Mirtazapine

Mirtazapine is an alpha-2 antagonist that is FDA-approved for the treatment of major depressive disorder (MDD).<sup>16</sup> Through its inhibition of alpha-2 adrenergic signaling, mirtazapine results in increased norepinephrine and serotonin release, as well as histaminergic receptor blockade.<sup>16</sup> The effects on these numerous neurotransmitters and receptors contribute to the hypothesized mechanism for the resulting increased appetite and weight gain seen with mirtazapine usage.<sup>17</sup> Mirtazapine is generally dosed at 15 mg once daily in the evening, then titrated to 30 mg once daily for desired effect or until no longer tolerated. Mirtazapine is generally well tolerated, with common adverse effects including weight gain, appetite stimulation, drowsiness, increased serum cholesterol, and constipation. Less common, but severe, adverse effects of mirtazapine include akathisia, arrhythmias, suicidal ideation, and serotonin syndrome.<sup>16</sup> Although appetite stimulation and weight gain are known side effects of mirtazapine, there are limited data on the agent used specifically for this desired outcome.

Theobald and colleagues performed an open-label, crossover trial of mirtazapine 15 mg and 30 mg in 20 cancer patients with pain

and other distressing symptoms.<sup>18</sup> The study analyzed the effect of mirtazapine on the endpoints of depression, pain intensity, appetite, insomnia, weight, and overall quality of life.<sup>18</sup> For the outcome of appetite stimulation, a numerical rating scale was used to assess the patient’s appetite over a weekly time period, while patient weights were recorded over the course of the study period. The mean number reported for appetite decreased from 3.9 at baseline to 3.2 at study end ( $p=0.10$ ). Although the change in appetite was not statistically significant, the authors reported a trend towards improvement at the week 7 study end.<sup>18</sup> Mean weight gain from the study outset to week 4 was 2.6 pounds, and the mean weight gain from study outset to the week 7 study end was 2.0 pounds. Improvements in all symptoms studied were seen across both the 15 and 30 mg dosages. While the increases in appetite and weight gain are not substantial, the authors argue that untreated patients could be expected to have worsened over a similar time period.<sup>18</sup>

Riechelmann et al. conducted an open-label, phase II, single-institution trial of mirtazapine in non-depressed patients with cancer-related cachexia/anorexia.<sup>19</sup> Mirtazapine was administered at 15 mg once daily at bedtime for 3 days, and if tolerated, subsequently increased to 30 mg once daily at bedtime.<sup>19</sup> The open-label period of the study was carried out for 8 weeks, and at the 4-week intent-to-treat analysis, 17 patients were evaluable. Appetite was assessed using the Edmonton Symptom Assessment Scale (ESAS), which includes an item for appetite on a scale of 0 to 10.<sup>19</sup> For the primary endpoint of weight gain, 4 of 17 patients had weight gain of 1 kg or greater (median 1.5 kg, range 1 – 3.6 kg).<sup>19</sup> Of the 4 patients that responded to mirtazapine therapy, all had an improvement in the ESAS assessment by at least 2 points. Mirtazapine was generally well tolerated, with 2 patients withdrawing secondary to toxicities including dizziness, blurred vision, drowsiness, and dry mouth.<sup>19</sup>

### Steroids

Though the full mechanism of action in appetite stimulation is not fully elucidated, corticosteroids are thought to reduce proinflammatory cytokines.<sup>17</sup> Increased appetite is also a well-known side effect of steroid use, so using these agents as appetite stimulants follows logically.

Several studies have been published using corticosteroids for appetite stimulation. In 1984, Willox et al. explored prednisolone as an appetite stimulant in 61 patients with various solid tumors. Patients received either prednisolone or placebo and then crossed over to the other group.<sup>20</sup> Regardless of order, patients receiving prednisolone reported statistically significant improvements in appetite; however, weight gain was not statistically significant between groups.<sup>20</sup> Other trials have found similar outcomes, with improvement in appetite on steroids but no significant weight gain.<sup>20-24</sup> In 1985, Bruera and colleagues published a randomized, double-blind, crossover trial that compared 32 mg of methylprednisolone (MP) with placebo in 40 terminally-ill cancer patients.<sup>21</sup> Appetite was increased in 68% of patients who received MP, but weight gain was not reported in these patients. Of note, appetite was also improved in 77% of patients who received placebo.<sup>21</sup>

Studies with dexamethasone for appetite stimulation have also produced mixed results. As described above, Loprinzi and

colleagues randomized patients to receive dexamethasone 0.75 mg four times daily, megestrol acetate 800 mg/day, or fluoxymesterone 10 mg twice daily. In this study megestrol and dexamethasone had similar improvements in appetite, but dexamethasone had a higher rate of side effects and discontinuation.<sup>11</sup> Inoue et al. also examined dexamethasone as treatment for delayed emesis, anorexia, and fatigue caused specifically by irinotecan.<sup>25</sup> Sixty-eight patients received either dexamethasone 8 mg daily on days 2-4 or placebo. All patients received dexamethasone plus a 5-HT3 antagonist for anti-emetic prophylaxis on day 1. Anorexia occurred less frequently in the dexamethasone group but the difference was not statistically significant.<sup>25</sup>

## Conclusion

While several agents—including megestrol, dronabinol, mirtazapine, and steroids—have been studied as appetite stimulants for cancer patients, overall data are mixed. Megestrol has the most positive data of agents studied, but is not without complications. Clinicians should consider patient characteristics and co-morbid conditions, as well as weighing risk vs benefit before starting any pharmaceutical agent for appetite stimulation in cancer patients.

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## Tables and Charts:

Summary of Agents Used for Appetite Stimulation in Cancer Patients			
Drug	Usual Dosage	Common Toxicities	Literature Quality
Megestrol acetate <sup>8-12</sup>	160 – 800 mg by mouth once daily	Headaches Insomnia Upset stomach/bloating General weakness	Randomized, double-blind, placebo-controlled trial Randomized, active controlled trial
Dronabinol <sup>14-15</sup>	2.5 – 5 mg by mouth prior to lunch and dinner	Dizziness Drowsiness Upset stomach General weakness	Randomized, placebo-controlled trial Randomized, active controlled trial
Mirtazapine <sup>18-19</sup>	15 – 30 mg by mouth once daily in the evening	Drowsiness Dizziness Hyperlipidemia Constipation	Open-label, dose escalation cross over Open-label, phase II trial
Corticosteroids Dexamethasone <sup>11</sup>	0.75 mg by mouth four times daily		Randomized, active-controlled trial
Prednisolone <sup>20</sup>	5 mg by mouth three	Hyperglycemia Hypertension Insomnia/irritability Impaired wound healing	Randomized, placebo-controlled trial Randomized, double-blind, crossover trial
Methylprednisolone <sup>21</sup>	16 – 32 mg daily divided in 3 – 4 doses		Randomized, double-blind, crossover trial

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# Getting the Skinny on Anorexia Nervosa in Pediatric Patients

By: Brian J. Catton, PharmD

## INTRODUCTION

Anorexia nervosa (AN) is a clinical diagnosis characterized by refusing to maintain body weight at or above the minimally normal level for age and height, as well as an intense fear of gaining weight and a disturbance in body image.<sup>1</sup> The prevalence of AN was once seen in wealthy, young Caucasian women, but is now becoming recognized in other population groups such as minorities, males, and countries where eating disorders were once unknown.<sup>2</sup> In the pediatric population, eating disorders (such as AN) are diagnosed more than type 2 diabetes with a peak onset between 13 and 18 years of age, and a national prevalence of AN ranging from 0.5 to 2%.<sup>3</sup>

## ETIOLOGY

Although the cause of AN is not clearly defined, its onset is due to cultural, psychological, genetic, environmental, and biological factors.<sup>1,4</sup> The way females think and feel about themselves is pervasively impacted by how cultures portray and define what is an ideal weight and figure.<sup>2</sup> Some predisposing psychologic factors leading to AN include (but are not limited to) behavioral rigidity, perfectionism, and desire to be in control; in reality, the psychologic issues are more prominent than genetic influences on eating, hunger, or satiety.<sup>2,4</sup> Regarding genetic factors, patients who have first-generation relatives with AN are 7 to 12 times at a greater risk of developing AN themselves; additionally, twin studies have estimated AN heritability between 33% and 84%. Although the exact genetic mechanisms are unknown (i.e. specific genes on chromosomal regions), those regions tend to be activated during puberty.<sup>3,4</sup>

Concerning environmental factors, a large community cohort study has shown that dieters were five times more likely to develop AN than non-dieters, suggesting that dietary habits play a significant role in the onset of AN. Additionally, studies have shown that patients living in families who have sit-down meals together were less likely to develop AN than those who do not.<sup>2,3</sup> Physical hyperactivity, manifesting as restlessness, athleticism, or compulsive exercise, is associated with weight loss, most likely due to the hyperactivity of the hypothalamic-pituitary axis.

## CLINICAL PRESENTATION

The key feature in patients with AN is their refusal to maintain 85% of optimal body weight based on their age and height as depicted in growth charts published by the Centers for Disease Control and Prevention (CDC).<sup>2</sup> Several physical examination findings in identifying AN include, but are not limited to, the following: weight change over 6-12 months; unhealthy weight-control behaviors; body image distortion; symptoms of malnutrition; and distinct physical exam findings such as acrocyanosis, lanugo, and dry, pale, discolored skin (Table 1).<sup>3,4,5</sup> Patients with AN may present to their pediatrician with some additional medical complications (Table 2).<sup>1-5</sup> Long-term effects of malnutrition include but are not limited to osteopenia, structural changes in the brain, growth retardation (which may be permanent), and delayed pubertal onset.<sup>2,5</sup> The American Academy of Pediatrics lists several

criteria to admit patients with AN for hospitalization (Table 2)<sup>3</sup>. Different reliable screening tools and questionnaires are available for clinicians to better assess symptoms and disorders (Table 3)<sup>1,5</sup>. Most commonly, the SCOFF questionnaire screens the chances of eating disorders including AN (Table 4).<sup>5</sup> This five-item, closed-ended questionnaire detects the chances of patients developing AN, where responding “yes” to two or more questions indicates a very high chance of patients having AN. In order to make a definitive diagnosis, consulting the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) is essential. Unlike its predecessor, DSM-V focuses more on behavior rather than weight management, and also excludes the criterion for amenorrhea. The updated criteria includes:<sup>6</sup>

1. Restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health.
2. Intense fear of gaining weight or becoming fat, even though underweight.
3. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

## NEUROENDOCRINE ABNORMALITIES

### Serotonin (5-HT)

5-HT normally plays a substantial role in regulating appetite, mood, and stress. The lack of endogenous 5-HT results in hyperactivity, depression, and behavioral impulsivity.<sup>2,7</sup> Tryptophan, an essential amino acid and the precursor to 5-HT, is only available in diet. Excessive diet restrictions and malnutrition decreases 5-HT metabolites and stores in the brain (e.g. the metabolite 5-hydroxyindoleacetic acid). Also, dietary restriction induces an exaggerated feedback control over 5-HT synthesis and smaller tryptophan availability decreases neurotransmission at its postsynaptic sites. Consequently, compensatory upregulation of postsynaptic receptors (e.g. 5-HT<sub>1A</sub> receptors) results in increased sensitivity and may be involved in anxiety and appetite suppression.<sup>2,7</sup>

### Dopamine (DA)

DA mostly exerts its effects of regulating movement, feelings of pleasure, and emotions in the striatum of the brain. Altered striatal dopamine function may result in altered feeding behavior, anhedonia, dysphoric mood, and increased motor activity. Such imbalances may be traits that contribute to the susceptibility to developing AN rather than emerging secondary to malnutrition.<sup>8</sup>

### Norepinephrine (NE)

Norepinephrine affects the attention and response sections in the brain by regulating sympathetic activity that most people associate with the “fight or flight” response. However, excessive stimulation of the sympathetic nervous system and reduced cerebral blood flow increases NE metabolism, resulting in dysfunction of the insula section in the brain. Because of a malfunctioning insula, patients with AN are more likely to process a distorted self-awareness (e.g. perception of pain, vision, taste, and body

Table 1: Objective Effects and Medical Complications Associated with AN

System	Effects	System	Effects
Fluids/electrolytes	Dehydration Hypochloremic metabolic acidosis (in patients who use laxatives) Hypochloremic metabolic alkalosis (in patients who vomit) Hypokalemia Hypomagnesemia Hyponatremia Hypophosphatemia	Metabolic/endocrine	Amenorrhea Delayed onset of puberty Growth retardation Hypercortisolism Hypoglycemia Hypogonadism Hypothyroidism
Cardiovascular	Bradycardia EKG abnormalities Hypotension Orthostasis Syncope Systolic murmur or mitral valve prolapse	Musculoskeletal	Decreased bone mineral density Loss of subcutaneous tissue Low weight Muscle wasting
Gastrointestinal	Abdominal pain Delayed gastric emptying Elevated liver function enzymes Hypomotility causing constipation Postprandial fullness Scaphoid abdomen with stool palpable in lower left quadrant Vomiting with superior mesenteric artery syndrome	Neurologic/psychiatric	Abnormal EEG Anxiety Cognitive and memory dysfunction Cortical atrophy (decreased gray and white matter) Depression Obsessive-compulsive disorder Post-traumatic stress disorder Seizures
		Hematologic	Anemia Leukopenia Thrombocytopenia Dehydration High urine output Pyuria

Table 2: American Academy of Pediatrics Criteria for Inpatient Hospitalization in AN

< 75% ideal body weight or ongoing weight loss despite intensive management
Arrhythmia
Body fat < 10%
Failure to respond to outpatient treatment
Heart rate < 50 bpm daytime (< 45 bpm nighttime)
Orthostatic changes in pulse (>20 bpm) or blood pressure (> 10 mmHg)
Refusal to eat
Systolic blood pressure < 90 mmHg
Temperature < 96°F

scheme). Furthermore, consequent starvation results in nutritional depletion of NE precursors, specifically tyrosine, and reinforces AN behaviors, especially anxiety.<sup>9</sup>

#### Leptin

Leptin is a circulating hormone produced in adipose tissue that regulates weight and energy by mediating neuroendocrine function. This hormone is sensitive to concentrations to the acute metabolic effects of decreased caloric intake and decreased energy. In AN patients, leptin levels remain low due to low levels of circulating fat and depleted body fat stores, signaling starvation to the brain and induces hyperactivity.<sup>2,4</sup>

## PROGNOSIS

Along with other prognostic factors, the lifetime prevalence of depression and anxiety disorders in patients with AN is 50-68% and 30-65%, respectively (Table 4).<sup>2</sup>

<sup>4</sup> The mortality risk of patients diagnosed with AN within 10 years is 10%, mostly due to starvation or suicide.<sup>2,4</sup>

## TREATMENT

### Initial Therapy

Because of the neurobiology and resultant mind-set of a patient with AN, patients cannot be reached by logical explanations

of the consequences of their illness and will commonly resist treatment.<sup>2,10</sup> Initially, the primary goal is to reestablish nutritional status and resolve medical complications via enteral, parenteral, or oral nutrition (depending on gut function).<sup>2</sup> Regarding weight gain, inpatients should gain about 0.3-0.4 pounds per day, whereas outpatients should gain 1-2 pounds per week. In order to prevent refeeding syndrome, clinicians should titrate and increase their total daily caloric intake very slowly. Once their energy requirements are met, their metabolic rate will normalize and gastrointestinal function will be restored.<sup>2</sup> Once patients have stopped losing weight, they can go either to a supportive home

Table 3: Tools and Questionnaires Used

Name	Abbreviation	Length	Format	Target Audience	Measured Outcome
Children's Somatization Inventory	CSI	19 items	5-point Likert scale	6-18 years of age	Breadth and severity of somatic symptoms
Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III version	QPGS-RIII	63 items	5-point Likert scale	10 years of age and older	Frequency, severity, and duration of gastrointestinal
Screen for Child Anxiety-Related Emotional Disorders	SCARED	41 items	3-point Likert scale	9-18 years of age	Presence of anxiety disorders

Table 4: The SCOFF Questionnaire

Factor	Question
Sick	Do you make yourself Sick because you feel uncomfortably full?
Control	Do you worry you have lost Control over how much you eat?
One stone	Have you recently lost more than One stone (14 lbs. /6.3 kg) in a 3-month period?
Fat	Do you believe yourself to be Fat when others say you are too thin?
Food	Would you say that Food dominates your life?

Table 5: Factors Affecting AN Prognosis

Favorable Prognosis	Unfavorable Prognosis
Better parent-child relationship	More significant weight loss
Earlier onset of age	Purging behavior
Shorter duration of symptoms	Physical hyperactivity

(where they can continually work with a dietician and therapist); if unable, they can go to a day treatment program for continual monitoring. The patient may still deal with persistent anxiety and other psychiatric conditions despite the resolution of their weight and nutritional status.<sup>2</sup>

#### Nonpharmacologic Therapy

Once the patient becomes stabilized, cognitive and psychological factors that led to their eating disorder must be addressed. Family-based therapy (FBT) for patients in supportive families is first-line treatment to decisively resolve AN.<sup>2,3,5</sup> FBT usually lasts between 6 to 12 months and involves three phases: physical recovery; behavioral recovery; and psychological recovery. In physical recovery, parents are empowered to ensure the patient is adequately eating and reaching 85% of their normal weight based on CDC growth charts (contrary to previous models that have blamed parents, which is becoming obsolete).<sup>2,3,10</sup> In behavioral recovery, clinicians empower patients to take responsibility for their own diet to ensure their daily caloric requirements are met. In psychological recovery, clinicians empower the entire family to resume normal developmental stages for the patient. Studies have shown that 50-60% of patients with AN who are committed to FBT achieve full remission within one year, and another 25-35% show improvement, but not remission.<sup>3</sup> In cases where the patient has been abused, they can pursue cognitive behavioral therapy (CBT) or interpersonal therapy (IPT) to address psychological factors. CBT teaches patients strategies to cope with feelings that initially led them to AN, whereas IPT focuses on interpersonal problems that may play a role in AN behaviors.<sup>2</sup>

#### Pharmacologic Treatment

Currently, no medications are granted approval by the Food & Drug Administration in treating AN due to weak or insufficient evidence (i.e. no randomized controlled trials conducted in children or adolescents alone); however, some medications are recommended only for co-occurring psychiatric conditions.<sup>2-4</sup>

The selective serotonin reuptake inhibitors that effectively treat depression and OCD, but do not resolve weight restoration, are fluoxetine and citalopram. Physicians must be careful in prescribing these medications due to the Black Box Warning of increased risk of suicidal thinking and behavior in children and adolescents taking antidepressants for various psychiatric disorders.<sup>11</sup> Tricyclic antidepressants (i.e. clomipramine and imipramine) have shown increased appetite, but are not recommended due to their adverse effect profiles and insignificant effect on weight gain. Growth hormones and testosterone have shown improvements in behavior, but no improvements in weight gain.<sup>2</sup>

Among the atypical antipsychotics, only four have published case reports or case series; although no weight gain was reported, there was some improvement in psychiatric conditions. Olanzapine among patients with AN has shown to be equally effective compared to patients with AN only undergoing CBT. Concerning quetiapine, patients with AN, that were studied demonstrated improved depression and anxiety. Although risperidone has shown a decline in anxiety and obsessive behavior in some case series, a double-blind, placebo-controlled study of risperidone for treating patients with AN did not show an additional benefit.<sup>3,12</sup> Lastly, a case series involving aripiprazole showed improvement in anxiety and depression, along with decreased distress and obsessional symptoms.<sup>2</sup>

#### Conclusion

As pharmacists, we are entrusted with the responsibility to care for all patients irrespective of gender, culture or dietary lifestyle. Although pharmacists in a community setting may not be able to provide nutritional support, we can be quick to identify pediatric

patients who may need referrals for nutritional support and psychological services. Since we are strategically positioned to ensure those who may assist in care and proper transitions of care, we must be quick to identify concerning signs and symptoms to address to the patients' caregivers and provide them the necessary help. As they receive nutritional and psychological support, pediatric patients with anorexia nervosa will learn to accept themselves for who they are.

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## Current Landscape in Parenteral Nutrition

Malgorzata Slugocki, Pharm D; Rachel L. Rivera, Pharm D, MHA, BCACP  
Fairleigh Dickinson University School of Pharmacy

**Learning Objectives:**

**After participating in this activity, the participant shall be able to:**

**Pharmacist:**

1. Define parenteral nutrition.
2. Identify patients who can benefit from parenteral nutrition.
3. Name common sources and commercially available solutions of macronutrients.
4. Describe the caloric contribution from each macronutrient.
5. Describe benefits and possible risks of lipid administration.
6. Differentiate between the routes of administration of total parenteral nutrition and name the concentrations limits that need to be observed.

**Pharmacist Con't**

7. Describe the macro- and micronutrient requirements for adult and pediatric patients.
8. Describe the present challenges in of parenteral nutrition prescribing and preparations.

**Pharmacy Technician:**

1. Define parenteral nutrition.
2. Identify patients who can benefit from parenteral nutrition.
3. Name common sources and commercially available solutions of macronutrients

**Author disclosures: None to disclose****Activity type: Knowledge**

UAN: 0136-0000-15-032-H04-P

0136-0000-15-032-H04-T

Release date : 12/14/15; Expiration: 12/14/18

**ABSTRACT**

Nutritional support is crucial in patients who cannot appropriately maintain nutritional status. The area of parenteral nutrition today is challenged by the lack of standardized ordering process, complex compounding process, and a high rate of errors occurring in all steps of PN preparation and delivery. This article aims to review the current trends and challenges in the process of parenteral nutrition compounding and delivery.

**INTRODUCTION**

Nutritional support is crucial in patients who cannot appropriately maintain nutritional status due to ingestion or absorption abnormalities, or in critically ill patients who require maintenance of nutrition and metabolic status secondary to injury, infection or severe inflammation<sup>(1)</sup>. Treatment plans for acutely or chronically undernourished patients have included nutritional support since the late 1960s<sup>(2)</sup>. Decision to initiate nutritional support should be made after a thorough nutritional assessment, and is usually appropriate in any patient whose clinical condition has a potential for causing severe malnutrition. Critically ill patients, those on a ventilator, or patients under severe metabolic stress are normally candidates for parenteral nutrition (PN).

The nature of parenteral nutrition preparation and delivery is a complex and expensive process requiring involvement of clinicians from multiple professions. A PN product is a sterile preparation that is delivered intravenously. Ideally, It should contain an optimal combination of macronutrients and micronutrients to satisfy a patient's specific nutritional requirements. The macronutrients include protein, carbohydrates, lipids, and water. The micronutrients include the electrolytes, trace elements, and vitamins.

The area of PN today is challenged by the lack of standardized ordering process, complex compounding process, and a high rate of errors occurring in all steps of PN preparation and delivery. Despite progress made in this area, there is still need for better assessment and recognition of the needs of malnourished patients<sup>(3)</sup>. This article aims to review the current trends and challenges in the process of PN compounding and delivery.

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N) Board of Directors in 1993 and 2002 published the "Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients" to support practitioner and patient choices in determining appropriate clinical care. The benefit of these guidelines was their applicability to multiple patient settings including inpatient and ambulatory care venues. In 2009, A.S.P.E.N. began to set forth serial guidelines for the management of PN in various scenarios such as adults with hyperglycemia, pediatric patients with intestinal failure, and neonates at risk for metabolic bone disease<sup>(4-6)</sup>. The purpose of the updated guidelines is to provide guidance in juxtaposition with professional judgment to meet the nutritional needs of patients in a variety of clinical circumstances.

## SUMMARY OF ESTABLISHED RECOMMENDATIONS

### Candidates For Parenteral Nutrition

Clinical trials comparing enteral nutrition (EN) to PN in critically ill patients demonstrate that for patients with intact gastrointestinal function, enteral nutrition is preferred due to decreased risk of complications from infection<sup>(7)</sup>. Adult patients in whom PN may be indicated include those who are either unable to absorb nutrients from the gastrointestinal tract, undergoing cancer treatment, critically ill, have an eating disorder, or are experiencing hyperemesis gravidarum<sup>(8-11)</sup>. Pediatric candidates for PN include those with intestinal failure, lack of adequate nutrient supply via oral or enteral routes, a clinically labile condition receiving extracorporeal membrane oxygenation (ECMO), or hypercatabolic nutritional state<sup>(12, 13)</sup>.

In general, PN may be continued until a feasible transition to enteral feeding is attainable, preferably as soon as possible.

Table 1 summarizes general requirements of macro- and micronutrients in pediatric and adult populations.

Adult and pediatric macro- and micronutrient requirements<sup>(14-21)</sup>.

		<b>Adults</b>	<b>Pediatrics</b>	
	Caloric Requirement	20-25 kcal/kg/day	Preterm neonate < 6 months 6 – 12 months 1 – 7 year 7 – 12 year 12 – 18 year	90 – 120 kcal/kg 85 – 105 kcal/kg 80 – 100 kcal/kg 75 – 90 kcal/kg 50 – 75 kcal/kg 30 – 50 kcal/kg
Macronutrients	Amino Acids	0.8-1.0 g/kg/day	Preterm neonate Term infant Children 1 – 10 years) >10 year	3 – 4 g/kg/day 2 – 3 g/kg/day 1 – 2 g/kg/day 0.8 – 1.5 g/kg/day
	Dextrose	≤7mg/kg/min	Preterm neonate Term infant Children 1 – 10 year > 10 year	8 – 10 mg/kg/min 12 mg/kg/min (max 14-18) 8 – 10 mg/kg/min 3.5 mg/kg/min
	Lipids	1 g/kg/day	Premature infant  Term infant  Children 1 – 10 year > 10 year	3 – 3.5 g/kg/day (Max 0.17g/kg/hr) 3 g/kg/day (Max 0.15 g/kg/hr) 2 – 3 g/kg/day 1 – 1.5 g/kg/day
Micronutrients				
Electrolytes	Calcium	10 – 15 mEq/day	Premature infant Other	2 – 4 mEq/kg 1 – 2.5 mEq/kg
	Magnesium	8 – 20 mEq/day	0.25 – 1 mEq/kg	
	Potassium	1 – 2 mEq/kg*	2 – 5 mEq/kg	
	Phosphorous	20- 40 mmol/day	Premature infant Other	1 – 2 mmol/kg 0.5 – 1 mmol/kg
	Sodium	1 – 2 mEq/kg*	2 – 6 mEq/kg	
	Acetate	As needed to maintain acid-base balance	--	
	Chloride	As needed to maintain acid-base balance	2 – 6 mEq/kg	
Trace Elements	Zinc	2.5 – 4 mg/day	Premature infant Other	300 – 400 mcg/kg 50 – 250 mcg/kg
	Copper	0.5 – 1.5 mg/day	20 mcg/kg (max, 300 mcg)	
	Chromium	10 – 15 mcg/day	0.14 – 0.2 mcg/kg	
	Manganese	0.15 – 0.8 mg/day	1 mcg/kg (max, 50 mcg)	
	Selenium	40 – 120 mcg/day	1.5 – 3 mcg/kg (max, 30 mcg)	
	Iodine	--	1 mcg/kg	
	Molybdenum	--	0.25 mcg/kg (max, 50 mcg)	
	Iron	--	varies	

Table 1 Continued

		Adults	Pediatrics
Vitamins	Thiamin (B1)	6mg/day	0.2-1.4 mg/day
	Riboflavin (B2)	3.6 mg/day	0.3-1.6 mg/day
	Pyridoxine (B6)	6mg/day	0.1-2 mg/day
	Cyanocobalamin (B12)	5 mcg/day	0.4-2.8 mcg/day
	Niacin (B3)	40 mg/day	2-17 mg/day
	Folic Acid	600mcg/day	65-500 mcg/day
	Pantothenic acid (B5)	15mg/day	1.7-7 mg/day
	Biotin	60mcg/day	5-35 mcg/day
	Ascorbic acid (vitamin C)	200mg/day	40-115 mg/day
	Vitamin A	3300 IU/day	400-1200 mcg/day
	Vitamin D	5 mg/day	10-15 mcg/day
	Vitamin E	10 IU/day	4-19 mg/day
	Vitamin K	150/day	2-75 mcg/day

\*Multiple salts of these electrolytes may be provided for a total of 1 – 2 mEq/kg

## PN Components

### Amino acid solutions

Commercially available crystalline amino acid products are divided into standard formulations, designed for patients with normal organ function and nutritional requirements, as well as modified solutions suitable for patients who have altered protein requirements due to organ dysfunction or the clinical course of their condition (table 2).

Table 2. Commercially available crystalline amino acid solutions<sup>(21)</sup>.

Brand name	Type/Indication	Stock concentration
Aminosyn II	Standard	3.5%, 4.25%, 5%, 7%, 8.5%, 10%
Travasol	Standard	3.5%, 4.25%, 5.5, 8.5%, 10%
Aminosyn II	Standard/Fluid restriction	15%
Clinisol	Standard/Fluid restriction	15%
Novamine	Standard/Fluid restriction	15%
Prosol	Standard/Fluid restriction	20%
Hepatamine	Hepatic failure	8%
Hepatasol	Hepatic failure	8%
Aminosyn HBC	Metabolic stress	7%
Freamine HBC	Metabolic stress	6.9%
Branchamin (contains only leucine, isoleucine and valine to supplement standard amino acid base)	Metabolic stress	4%
Amino PF	Pediatric	7%, 10%
Trophamine	Pediatric	6%, 10%
Aminess (essential amino acids plus histidine)	Renal	5.2%
Aminosyn RF (essential amino acids plus arginine)	Renal	5.2%
Nephramine (essential amino acids plus histidine)	Renal	5.4%
Renamin (essential and some non-essential amino acids)	Renal	6.5%

### Carbohydrates

Carbohydrates are provided in the form of dextrose, and the 70% dextrose solution is the one mostly utilized in the compounding process, but other available concentrations (5%, 10%, 30%, and 50%) are appropriate as well. Non-insulin dependent sources of carbohydrate have been studied as an alternative to dextrose to improve glycemic control for patients with impaired insulin secretion or activity. Glycerol is a sugar alcohol alternative to dextrose, which provides 4.3 calories/gram. It is commercially available only as a 3% isotonic formulation with 3% amino acids and supplemental electrolytes (ProcalAmine®). A major disadvantage of this formula is the dilute amino acid and carbohydrate concentrations; most adult patients require between 3-4 liters of ProcalAmine® per day<sup>(22)</sup>.

### Lipids

Intravenous fat emulsions (IVFE) are used to provide 20-30% of total daily kilocalories and essential fatty acids<sup>(21)</sup>. The caloric contribution of fat is 9 calories per gram. The caloric content of available IVFE differs based on available concentrations (table 2,)<sup>(22)</sup>. The vitamin K content varies with manufacturer, with safflower oil formulations generally having less vitamin K than soybean oil products<sup>(22)</sup>.

Furthermore, IVFE products differ in their ratio of phospholipids and triglycerides<sup>(22)</sup>. Because higher amounts of circulating phospholipids are associated with impaired triglyceride clearance in neonates and infants, 20% IVFE is the preferred product for this population. Higher concentrated IVFEs (20% and 30%) have a lower phospholipid-to-triglyceride ratio compared with 10% IVFE.

IVFEs consist of several characteristics that make them a favorable medium for microbial growth: isosmotic tonicity, neutral-to-alkaline pH, and glycerol content. When IVFE fluids are added to dextrose-amino acid solutions to make total parenteral admixture (TNA), the potential for growth is decreased because of protective effects of hypertonic dextrose-amino acid solutions and decreased pH<sup>(23)(24)</sup>.

Several newer (new generation) parenteral lipid emulsions have been developed in the last 10-15 years, containing single-source lipid or blends of lipids. Emulsions containing pure olive oil (Clinoleic®), pure fish oil (Omegaven®), or different mixtures of soy, medium-chain triglycerides, olive and fish oil (Lipofundin®, SMOFlipid®, Lipoplus®) have been approved in Europe. These new generation lipid emulsions are being considered for approval in the US<sup>(25)</sup>.

Due to lack of commercially available unit volumes of lipids consistent with neonatal dose, institutions often repackage IVFE into syringes for infusion via syringe pump<sup>(24)</sup>. This has been found to increase microbial contamination, which can be reduced by the use of appropriate hang time of IVFE<sup>(24)</sup>. There is a slight discrepancy in the recommendations from the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) with respect to the duration of lipid infusion in pediatric patients. In order to ensure appropriate metabolic clearance and prevent lipid intolerance, the AAP recommends that the daily dose of IVFE be infused continuously over 18-24 hours<sup>(26)</sup>. However, in the guidelines prepared by a taskforce that comprised of CDC, AAP as well as other professional organizations, it is recommended that lipids alone should be infused within 12 hours in order to prevent catheter-related infections<sup>(27)</sup>. However the CDC or AAP do not address the infusion time of repackaged IVFE.

Due to the controversial nature of lipid administration guidelines, compliance with recommendations remains challenging.

Table 3. Energy and Vitamin K Content of commonly used IVFE<sup>(21)</sup>.

Lipid emulsion	Kcals/ml	Soybean oil, g/L	Safflower oil, g/L	Vitamin K, mcg/dL
Intralipid 10%	1.1	100	0	30.8
Intralipid 20%	2	200	0	67.5
Intralipid 30%	3	300	0	93
Liposyn II 10%	1.1	50	50	13.2
Liposyn II 20%	2	100	100	26
Liposyn III 10%	1.1	100	0	31
Liposyn III 20%	2	200	0	62
Liposyn III 30%	2.9	300	0	93

### Electrolytes

Electrolytes in PN formulations are necessary for maintenance of numerous cellular functions. They are generally added to either maintain normal serum concentrations, or to correct deficits<sup>(22)</sup>.

### Vitamins

Vitamins are available as adult and pediatric cocktails that differ in the content of vitamin K. Vitamin K supplementation should be considered in any patient requiring long-term (> 1 week) PN. The two available commercial vitamin products, Infuvite®, and MVI-Adult® include Vitamin K. There is also a product that does not contain vitamin K (MVI- Adult without vitamin K®), but its use is limited. IVFEs also contain vitamin K and may contribute significant amounts depending on the rate of infusion and concentration of lipid<sup>(21)</sup>.

There are no commercially available IV multivitamin products designed to meet the special requirements of premature infants, including higher vitamin A and lower doses of vitamins B1, B2, B6, and B12.

There is also uncertainty in 2012 ASPEN recommendations whether the vitamin D content of parenteral multivitamins is adequate to meet current recommended daily allowances, and the organization promotes the development of a parenteral vitamin D product for PN patients unresponsive to vitamin D supplementation<sup>(20)</sup>. The recommendations also emphasize the importance of supplementation with carnitine in neonatal PN<sup>(21)(20)</sup>.

### Trace elements

Clear deficiency syndromes have been demonstrated for cobalt (vitamin B12), copper, iodine, iron, and zinc, although seventeen trace elements have been identified as biologically important. Current recommendations also require supplementation with chromium, manganese, and selenium<sup>(21)</sup>.

### Commercially available preparations

In light of the recent drug shortages, many institutions have seen an increased usage of the premixed formulas. A study conducted at Boston Medical Center found that although the use of these formulas may be cost- and time - effective, it did not meet patients' protein requirements and resulted in a higher rate of electrolyte abnormalities, specifically hyponatremia<sup>(28)</sup>. Another study comparing the custom versus standardized formulation observed the cost saving benefit in hospitals that treat more than 15 patients per day<sup>(29)(30)</sup>.

Clinimix® and Clinimix E® are standardized parenteral nutrition formulations that can be substituted for custom formulas in patients requiring parenteral nutrition (tables 3 and 4). All Clinimix® formulations are available as either 1L or 2L bags<sup>(31)(32)</sup>. A three-in-one PN has become commercially available in Europe (Numeta®). It is a three-chamber system for use in pediatric and neonatal population. Each chamber contains a single macronutrient: glucose (13%, 16%, or 19%), a pediatric amino acid solution (Primene®) with electrolytes and olive oil-based lipid emulsion (ClinOleic®). The bag also gives ability to withhold lipids by keeping the seal unbroken between the lipid emulsion and the rest of the components<sup>(33)</sup>.

Table 4. Components of standardized parenteral nutrition, Clinimix E<sup>(31)</sup>.

Ingredient	*Clinimix E 2.75/5	Clinimix E 2.75/10	Clinimix E 4.25/5	Clinimix E 4.25/10	Clinimix E 4.25/25	Clinimix E 5/15	Clinimix E 5/20	Clinimix E 5/25
Dextrose, g/L	50	100	50	100	250	150	200	250
Amino acids, g/L	27.5	27.5	42.5	42.5	42.5	50	50	50
**Sodium, meq/L	35	35	35	35	35	35	35	35
**Potassium, meq/L	30	30	30	30	30	30	30	30
**Magnesium, meq/L	5	5	5	5	5	5	5	5
**Chloride <sup>1</sup> , meq/L	39	39	39	39	39	39	39	39
**Calcium, mmol/L	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
**Phosphate, mmol/L	15	15	15	15	15	15	15	15
**Acetate <sup>2</sup> , meq/L	51	51	70	70	70	80	80	80
Calories, kcal/L	280	450	340	510	1020	710	880	1050

\*Clinimix E 2.75/5: 2.75% Amino acid with electrolytes in 5% dextrose with calcium, sulfite-free injection

\*\*Balanced by ions from amino acids

<sup>1</sup>Contributed by lysine hydrochloride

<sup>2</sup>Derived from glacial acetic acid (for pH adjustment)

Table 5. Components of standardized parenteral nutrition, Clinimix<sup>(32)</sup>.

Ingredient	*Clinimix 2.75/5	Clinimix 4.25/5	Clinimix 4.25/10	Clinimix 4.25/20	Clinimix 4.25/25	Clinimix E5/15	Clinimix 5/20	Clinimix 5/25
Dextrose, g/L	50	50	100	200	250	150	200	250
Amino acids, g/L	27.5	42.5	42.5	42.5	42.5	50	50	50
**Chloride <sup>1</sup> , meq/L	11	17	17	17	17	20	20	20
**Acetate <sup>2</sup> , meq/L	24	37	37	37	37	42	42	42
Calories, kcal/L	280	340	510	850	1020	710	880	1050

\*Clinimix 2.75/5: 2.75% Amino acid in 5% dextrose, sulfite-free injection

\*\*Balanced by ions from amino acids

<sup>1</sup> Contributed by calcium chloride, lysine hydrochloride, magnesium chloride, and sodium chloride

<sup>2</sup> Derived from glacial acetic acid (for pH adjustment) and sodium acetate

### Routes Of Administration And Type Of Access

Parenteral nutrition can be administered via central or peripheral routes. The peripheral route is suitable for short-term (less than 2 weeks) nutrition of moderately stressed patients requiring < 1800 kcal/day. It carries limits on the concentration of amino acids and dextrose as well as the osmolality of the solution due to the risk of thrombophlebitis<sup>(34)</sup>. Furthermore, due to dilute nature of peripheral parenteral nutrition, IVFE are usually administered as a piggyback. The central route allows for infusion of solutions that are > 900mOsm/L, as well as long-term administration. It is also the preferred route for home PN administration<sup>(21)(22)</sup>.

### Preparation Of PN

The process of compounding PN must follow the guidelines from the <797> chapter in the USP, and must be prepared in a device that meets International Organization for Standardization (ISO) class 5 standard<sup>(22)</sup>. An automated compounder is usually employed to admix nutrient stock solutions. The compounders have capabilities to perform calculations necessary to determine volumes of the stock solutions for PN formulations<sup>(22)</sup>.

PN is compounded as either a two-in-one or three-in-one formulation (TNA). The two-in-one formulation includes amino acids and dextrose, and the three-in-one preparation consists of all three macronutrients delivered via one bag. The inclusion of lipids in the preparation is associated with an increased risk for infections<sup>(33)</sup>.

### CURRENT LANDSCAPE

#### Stability/Incompatibility

Because of IVFE content, TNAs demonstrate a greater stability challenge<sup>(22)</sup>. Compounded dextrose-amino acid solutions are usually stable for 30 days under refrigeration at 4°C (39°F) and protected from light<sup>(22, 23)</sup>. To reduce the risk of microbial contamination, the <797> USP guidelines recommend storage of not more than 9 days under refrigeration (2-8°C [68°-77°F]) of all PN preparations<sup>(35)</sup>.

Ready-to-make solutions have a longer shelf life than the compounded preparations; manufacturer's guidelines should be followed regarding specific dates, temperature ranges, and storage conditions<sup>(23)</sup>.

Complex nature of PN compounding increases the risk of chemical and physical incompatibilities. Examples of these are the formation of crystalline matter (solid precipitate), as well as phase separation with the liberation of free oil in preparations containing lipid solutions (liquid precipitate). Examples of these dangerous solid incompatibilities, which can result in embolic death include dibasic calcium phosphate and calcium oxalate<sup>(23)</sup>. A number of interventions have been shown to avoid the formation of these precipitates, with the most effective one being the maintenance of appropriate order of compounding: adding potassium or sodium phosphate injections first and calcium near the end of the compounding sequence<sup>(36)</sup>.

Additional risks of forming solid precipitates include the use of bicarbonate salts when indicated to correct a base deficit through PN, which may result in the formation of calcium carbonate<sup>(23)</sup>.

Phase separation and liberation of free oil can occur when excess of cations is added to a TNA formulation<sup>(23)</sup>. Trivalent cations such as Fe+3 are the most disruptive. Even the order of compounding may cause instability of the TNA<sup>(23)</sup>. Because of this, there is no safe concentration of iron dextran in any formulation. In general, the compounding process should not place destabilizing cations in close sequence with minimally diluted IVFE<sup>(23)</sup>.

Furthermore, the problem of emulsion instability may be partially reduced by using standardized formulations that are documented to have physicochemical stability<sup>(23)</sup>.

Pharmacists should follow instructions from the manufacturers as well as the automated compounders to ensure optimal and stable preparation<sup>(23)</sup>.

#### **Errors/Omissions/Lack of order standardization**

PN is classified as a high-alert medication according to the Institute for Safe Medication Practices (ISMP)<sup>(37)</sup>. However, only 58% of organizations have precautions in place to prevent errors and patient harm associated with PN<sup>(38)</sup>. Many health care settings that produce PN exhibit inconsistencies in the knowledge and skills of the healthcare professionals responsible for PN prescribing, review, compounding, and administration<sup>(39)</sup>.

In September 2013, ASPEN hosted a multi-organizational and inter-professional safety summit, which resulted in a document delineating recommendations based on practices that are generally accepted to minimize errors associated with PN<sup>(39)</sup>. One of the areas that contribute to errors and increase potential for serious complications is the lack of a computerized standardized ordering process for PN<sup>(39)</sup>. This computerized standardized system should address all aspects of PN prescribing including order entry and transcription<sup>(39-41)</sup>. The organization also encourages dedication of properly trained personnel to regularly perform the tasks associated with PN processing. Furthermore, institution-specific duration of PN orders should be established as well as monitoring parameters and frequency. Health care organizations should have policies and protocols that allow for order modification in case of incompatibilities<sup>(39)</sup>.

Other important areas of concern include the software inability of automated compounders to establish catastrophic limits of electrolytes, as well as using adult-programmed software/compounders to prepare neonatal/pediatric solutions<sup>(42)</sup>. Additional common errors include the use of unapproved abbreviations and dose designations, catheter misconnections, measurement errors involving tuberculin and insulin syringes, and mix-ups between products or product concentrations<sup>(42)</sup>.

The guidance from ASPEN provides detailed recommendations regarding the verification, compounding, and administration processes, as well as examples of clear and comprehensive PN order and labeling templates<sup>(39)</sup>.

#### **Drug shortages**

Shortages of parenteral nutrition components have been occurring sporadically since 1988<sup>(43)</sup> until 2010 when the shortages became more pronounced, consistent, and involving almost all components of PN except hypertonic dextrose<sup>(43)(44)</sup>. There are several factors contributing to this problem: limited number of companies producing sterile products, quality issues requiring remediation or discontinuation of production, as well as manufacturing issues. In 2012 the FDA created the Safety and Innovation Act, which requires manufacturers to notify FDA of upcoming shortages and discontinuations<sup>(43)</sup>. This decreased the shortages to some degree but continues to be an ongoing challenge<sup>(44)</sup>. Clinicians must be cognizant of shortages and monitor for them, which increases the overall cost and time involved in the care of the patient<sup>(44)</sup>. An example of the devastating effects of PN components' shortages is the incident of 9 deaths associated with *Serratia marcescens*-contaminated PN formulation. The pharmacy was unable to obtain amino-acids due to shortage, and prepared amino acids from source powders and water<sup>(44)</sup>. PN shortages also contribute to other negative outcomes such as increased catheter-related infections, electrolyte abnormalities, administration errors, and an overall reduced access to quality healthcare. Providing PN during drug shortage continues to pose challenges for all professionals involved in the entire process of PN preparation and delivery. Clinicians must carefully assess this process and remain vigilant<sup>(44)</sup>.

#### **Home Infusion**

Increasing health care costs and the focus on improving quality of life have resulted in an increased utilization of home parenteral nutrition therapy.

The advantages of home PN include improved quality of life, reduction of exposure to hospital-borne pathogens, ability to continue work and daily activities, and reduced overall expenses<sup>(45)</sup>. Disadvantages include possibility of inadequate education, dehydration, re-hospitalization, noncompliance, lack of immediate access to health care personnel, and delay in obtaining laboratory results<sup>(45)(46)(47)(48)</sup>.

#### **TOPICS FOR FURTHER RESEARCH**

According to ASPEN, further research/discussion is needed regarding such topics as computerized order standardization, documenting errors, training of personnel, pre-mixed commercial products, reducing costs, and in general identifying strategies to reduce risks associated with PN prescribing, verification, compounding, and administration<sup>(39)</sup>.

## CONCLUSIONS

Parenteral nutrition is a valuable therapeutic intervention. PN component shortages continue to be challenging to clinicians who must exercise greater caution and invest more time in the care of a PN patient.

There remains a need for a standardized approach that will enhance communication among professionals. This, in turn, will reduce errors associated with prescribing, compounding, and administering PN preparations.

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\*Authors acknowledge Julie Kalabalik, PharmD,BCPS for contributing to the article



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**Continuing Education Quiz**

1. Which of the following patients would be the best candidate for a parenteral nutrition solution?
  - a. A pregnant patient with an eating disorder
  - b. A pediatric patient who is underweight
  - c. An adult patient post-surgery with a functioning GI tract
  - d. An elderly patient with a functioning GI tract who is malnourished
2. What is the daily protein requirement for an adult patient starting on parenteral nutrition?
  - a. 0.8-1 g/kg\*
  - b. 5g/kg
  - c. 0.1 g/kg
  - d. 4g/kg
3. Which of the following solutions would be the best choice for a patient who is under metabolic stress?
  - a. Renamin®
  - b. Hepatamine®
  - c. Clinisol®
  - d. Branchamine®
4. Prolonged lipid infusions may increase the risk for which of the following conditions?
  - a. Vein thrombosis
  - b. Tissue necrosis
  - c. Catheter-related infections
  - d. Infusion site reactions
5. The parenteral nutrition compounding process must follow
  - a. 797 chapter of the USP guidelines
  - b. ISMP guidelines
  - c. ASPEN guidelines
  - d. ISO guidelines
6. What is the stability of a compounded dextrose-amino acid preparation according to <797> USP guidelines?
  - a. 30 days room temperature
  - b. 9 days refrigerated
  - c. 14 days room temperature
  - d. 60 days refrigerated

**Passing Score is 70% or above**

**Please circle your answers (one answer per question)**

1. A B C D
2. A B C D
3. A B C D
4. A B C D
5. A B C D
6. A B C D

**Program Evaluation – Must be completed for credit**

Please rate the following items on a scale from 1 (poor) to 4 (excellent).

- |                                   |   |   |   |   |
|-----------------------------------|---|---|---|---|
| 1. Overall quality of the article | 1 | 2 | 3 | 4 |
| 2. Relevance to pharmacy practice | 1 | 2 | 3 | 4 |
| 3. Value of the content           | 1 | 2 | 3 | 4 |

Please answer each question, marking whether you agree or disagree

4. The program met the stated learning objectives:  Agree  Disagree

**Impact of the Activity**

5. The information presented (check all that applies):  
 Reinforced my current practice/treatment habits  
 Will improve my practice/patient outcomes  
 Provided new ideas or information I expect to use  
 Adds to my knowledge
6. Will the information presented cause you to make any changes in how you do your job?  
 Yes  No
7. How committed are you to making these changes?  
(Not - Very) 1    2    3    4
8. Do you feel future activities on this subject matter are necessary and/or important?  
 Yes  No

**Follow-Up**

As part of our ongoing quality-improvement effort, we would like to be able to contact you in the event we conduct a follow-up survey to assess the impact of our educational interventions on professional practice. Are you willing to participate in such a survey?

- Yes  No

This lesson is a knowledge-based CE activity and is targeted to pharmacists and pharmacy technicians. This program has been approved for 1 contact hour of continuing education credit (0.1 CEU). UAN: 0136-0000-15-032-H04-P; 0136-0000-15-032-H04-T. Release Date: 12/14/15; Expiration Date: 12/14/18

To receive continuing education credit, please provide the following information:

CPE credit for successfully completed quizzes will be uploaded to CPE Monitor. CE statement of credits are available to be printed from CPE Monitor website within 60 days of NJPhA receipt of the completed exam and evaluation.

Circle correct test answers and return to:

**NEW JERSEY PHARMACISTS ASSOCIATION**

Attention: Journal C.E. Department, 760 Alexander Rd., PO Box 1, Princeton, NJ 08543-0001

**Note: Passing grade is 70% for each examination.**

Name (First, Last): \_\_\_\_\_

Phone Number: \_\_\_\_\_

Email: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

License No: \_\_\_\_\_ E-PID#: \_\_\_\_\_ DOB (MM/DD): \_\_\_\_\_

**Payment Information:**

Enclosed is:  NJPhA Member (**FREE**)  \$15.00 Non-member

VISA       Master Card       American Express       Discover

Card Number: \_\_\_\_\_

Security Code: \_\_\_\_\_ Expire date: \_\_\_\_\_

Amount of charge: \_\_\_\_\_ Signature: \_\_\_\_\_

Check enclosed: Payable to NJPhA

Check # \_\_\_\_\_ Amount: \_\_\_\_\_

N/A, my NJPhA membership is currently up-to-date

OFFICE USE ONLY      DATE: \_\_\_\_\_ GRADE: \_\_\_\_\_

Membership: \_\_\_\_\_

# Highlights from the 145<sup>th</sup> Convention

By Lisa Sarachman, Communications & Content Management Associate

A big thank you to everyone who participated in our 145<sup>th</sup> Annual Meeting and Convention at Harrah's Atlantic City, October 16 – 18. The event was a huge success. This year, we had 150 pharmacist and pharmacy technician attendees from a wide range of practice areas including community (chain and independent), consulting, industry, hospital/ambulatory, military, and academia.

We were grateful to see the familiar faces of so many long-standing members. Their commitment to NJPhA - and willingness to impart their various skills and knowledge to advance the profession - is impressive and appreciated. There were many new faces this year as well, including students from NJ, PA and NY pharmacy schools. We are pleased to add many of these new faces to our member roster and look forward to their contributions on NJPhA committees, in NJPhA regions, and at continuing education activities over the coming year.

## A Year in Review

At the conference, our President, CEO, Board of Trustees, and Committee Chairs all reported on NJPhA's many accomplishments over the previous year.

Some highlights include the creation of a Social Committee and New Practitioner Committee. Watch for monthly emails regarding NJPhA's +TONIC Rx social events held in NJPhA's 6 regions throughout the year. We hope you will join us!

NJPhA also developed an intensive course for Consultant Pharmacists in the 2014-15 year. The ACPE-accredited *Preparing for a Consulting Pharmacy Career* course offers participants a 15 hour, 2-part practice-based activity with home study and live modules.

Finally, some of our biggest achievements were realized in the area of government affairs. Indeed, NJPhA made significant forward progress on legislative matters regarding biosimilars, safe disposal of opioids, medication synchronization, and pricing transparency.

## Continuing Education

Clearly, exceptional CE was a huge draw at this year's 145<sup>th</sup> Annual Meeting and Convention. We offered three certificate training programs over the three-day convention. We are proud that two of them – *Compounding Essentials* and *Preparing for a Consultant Pharmacist Career* – were developed and are offered exclusively by the NJPhA. In addition to three certificate training programs, convention attendees had the opportunity to earn 10 CE credits in topics ranging from transitional care and dermatology to medication errors and the Drug Supply Chain Security Act.

## Networking and Social Activities

In addition to *Finding Balance*, attendees also celebrated an "under the boardwalk" theme at Harrah's Atlantic City. After networking throughout the day in CE, at lunch, and during breaks,

pharmacy professionals found time to unwind at our Boardwalk Bash on Saturday evening, October 17. There, attendees enjoyed boardwalk-inspired games, music and dancing. Attendees also spent time in the NJPhA Historical Items Gallery complete with a mortar and pestle dating from 1870 - our founding year. More fun was had as pharmacy professionals crowded around NJPhA's PAC silent auction baskets. This year, we raised over \$1000!

## Awards and Winners

We witnessed a good number of victories over the weekend. In addition to the awards detailed on the inside front and back pages, we surprised three recipients with a new award that recognizes outstanding personal commitment and dedication to NJPhA. This first-time award was presented to RDC and its President and CEO, Larry Doud; Angelo Cifaldi, Esq.; and Satish Poondi, Esq.

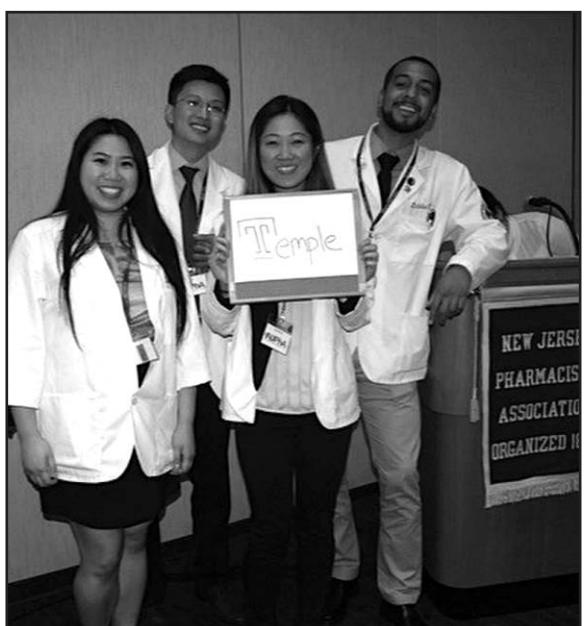
We are also happy to announce the winners of our CE competitions. With her rapid-fire savvy and first-rate patient consulting, Maribel DiPrimo won the "Know Pain, Know Gain" Pharmacy Patient Pain Counseling Competition. LIU Pharmacy students Shujaat Bhatti, Serena Chew, Muhammad Effendi, and Anne Marie Mathew took home the trophy for Saturday's Student Pharmacists Self-Care Championship. Congratulations everyone!

## Exhibitors and Sponsors

Finally, we would be remiss if we did not recognize this year's exhibitors and sponsors. We had a wide range of exhibitors this year. Organizations including government agencies, pharmacy product and service providers, and wholesalers joined us in the Exhibit Hall October 17 – 18. Especially with the help of our major sponsors and grant providers – AmerisourceBergen, Astra Zeneca, Kinray, Novartis, Pharmacists Mutual, RDC and Walgreens – the NJPhA was afforded a great opportunity to support New Jersey's pharmacy community and promote optimal patient care.

Please join us again at Harrah's in October 2016 when we celebrate "Keeping the Beat for NJ Pharmacy." As always, we look forward to seeing you there.

Enjoy our photo montage that follows!



# 2015 Convention Poster Presentations

The following posters were presented at the New Jersey Pharmacists Association 2015 Convention in Atlantic City, NJ, October 16-18, 2015. The non-peer reviewed abstracts indicate original presentations. The subsequent abstract indicates an encore presentation.

## IMPACT OF PALIPERIDONE PALMITATE ON HOSPITAL ADMISSIONS AND LENGTH OF STAY: A 4- YEAR MIRROR IMAGE STUDY IN AN ACUTE CARE SETTING. Hetty Cheng, Student, Rutgers University, Ernest Mario School of Pharmacy

**Abstract.** Non-adherence to medication is a major problem in all fields of medicine, particularly in psychiatry, and interventions that improve adherence may play a major role in improving the health of society at large. For patients with psychotic disorders such as schizophrenia, non-adherence to antipsychotic treatment is a predictor of relapse which could compromise the overall health of patients and have detrimental effects on their quality of life. The use of long-acting injectables (LAIs) is claimed to improve adherence and reduce relapse rates in comparison with the use of oral antipsychotics. LAI formulations require only bi-weekly or monthly injections from a health care provider, in contrast to daily self-administration of oral medication. This helps to resolve issues related to complicated treatment regimes that disrupt patients' daily routines and serve as constant reminders of their illness. LAIs may simplify the treatment regime and foster adherence for patients with cognitive improvement, improving long-term prognosis and reducing risk of relapse and rehospitalization, however current studies are few and varied so there exists a need to further evaluate the effectiveness of using LAIs in clinical settings. This study focuses on the potential benefits and obstacles in using a newer long-acting injectable, paliperidone palmitate, in the pharmacotherapy of psychiatric patients. This study aimed to evaluate the clinical utility and safe use of paliperidone palmitate (PP), a long-acting injectable antipsychotic in an acute care setting. This retrospective mirror-image study evaluated patients who were prescribed PP at Monmouth Medical Center 2 years prior to and 2 years after starting PP. Included patients were  $\geq 18$  years of age and received at least one dose of PP. Exclusion criteria included a CrCl  $< 50$  mL/min and pregnancy. Data was collected through retrospective chart reviews and analyses on readmission rates and length of stay was conducted. A total of 80 patients were included. Mean numbers of admissions per patient were 1.28 pre-injection and 1.05 post-injection. Total number of inpatient days were 939 pre-injection and 821 post-injection. Average length of stay was 9.21 pre-injection and 9.77 post-injection. There was a trend towards a decrease in the number of readmissions but an increase in average length of stay after relapse.

## SUPPRESSION OF BREAST CANCER STEM CELLS BY PTEROSTILBENE, AN ACTIVE COMPONENT OF BLUEBERRIES. Jeffrey Yang<sup>1</sup>, Joseph Wahler<sup>1</sup>, Agnes M. Rimando<sup>2</sup> and Nanjoo Suh<sup>1,3</sup>

<sup>1</sup>Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, USA

<sup>2</sup>United States Department of Agriculture, Agricultural Research Service, Natural Products Utilization Research Unit, University, MS, USA

<sup>3</sup>Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA.

**Abstract.** Breast cancer stem cells (BCSCs) are a subset of tumor cells that are believed to be responsible for the establishment and maintenance of tumors. Moreover, BCSCs are suggested to be the main cause of progression to metastasis and recurrence of cancer because of their tumor-initiating abilities and resistance to conventional therapies. Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a natural dietary compound found primarily in blueberries and *Pterocarpus marsupium* heartwood. As a dimethylated analog of resveratrol, pterostilbene has superior oral bioavailability in comparison to other stilbene compounds. Pterostilbene inhibits tumor formation and growth and metastasis by causing arrests in the cell cycle, inducing apoptosis, and promoting autophagy with negligible toxicity. In the present study, we examined the potential for pterostilbene to inhibit the tumor-initiating abilities of the cancer stem-like population in breast cancer. To determine the effects of pterostilbene on BCSC activity, the mammosphere cell culture system, which enriches for mammary progenitor cells and putative BCSCs (characterized as CD24-/low/ESA+), was utilized, using the estrogen-dependent MCF-7 breast cancer cell line. When mammospheres derived from the MCF-7 cells were treated with pterostilbene at 1, 10, and 20  $\mu$ M, a dose-dependent reduction in the number (measured by the mammosphere-forming efficiency, MFE) and size of the spheres was observed. Estrogen has been shown to expand the breast cancer stem-like cell population in estrogen-dependent breast cancer cell lines. Treatment of MCF-7 mammospheres with estrogen resulted in a shift to a more CD24-/low phenotype, which is associated with increased stemness. Pterostilbene at concentrations of 10 and 20  $\mu$ M reversed estrogen-induced expansion of MCF-7 BCSCs. Moreover, markers associated with proliferation of MCF-7 BCSCs such as pNFkB and cyclin D1 were reduced by pterostilbene. This study suggests that pterostilbene represses the breast cancer stem cell-like population, potentially contributing to the inhibition of breast cancer.

**THE USE OF INTRAVENOUS LIDOCAINE FOR ACUTE PAIN SECONDARY TO RENAL COLIC.** *Muhammad Effendi, Serena Chew, Pharmacy Interns, Long Island University*

**Abstract.** Lidocaine is a local anesthetic that provides analgesic effects by blocking voltage-gated sodium channels. Lidocaine has been shown to be an effective analgesic agent for a wide array of conditions such as post stroke pain, post herpetic neuralgia, neuropathic cancer pain, refractory headache, and severe intractable pain for hospice patients. The majority of literature pertaining to acute pain relief from renal colic are with opioids and NSAIDs. Due to potential adverse effects from these classes of medications, treatment with an alternative safe and effective agent may be needed. We describe the management of acute pain secondary to renal colic with intravenous lidocaine in a 29 -year-old male who presented to the emergency department. Lidocaine 150 mg was administered via intravenous piggyback over 20 minutes. The patient's pain was assessed via the use of the Visual Analogue Scale (VAS). Over 35 minutes, the patient's pain score decreased from a baseline of 8/10 to 2/10. There were no adverse effects reported by the patient. Our case report on the use of lidocaine for the management of acute pain secondary to renal colic adds to the limited literature currently available on this topic.

## Encore Poster

**PPAR $\gamma$  REGULATION OF THE PLACENTAL BCRP/ABCG2 TRANSPORTER.** *Yixin Lin<sup>1</sup>, Naureen Memon<sup>2</sup>, Kristin M. Bircsak<sup>1</sup>, and Lauren M Aleksunes<sup>1</sup>*

<sup>1</sup>Department of Pharmacology and Toxicology, Rutgers University Ernest Mario School of Pharmacy, Piscataway, NJ

<sup>2</sup>Department of Pediatrics, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

The breast cancer resistance protein (BCRP/ABCG2) is an ATP-binding cassette transporter that is expressed by syncytiotrophoblasts and plays a crucial role in extruding a wide range of substances to the maternal circulation. As part of the 'blood-placenta barrier, BCRP protects the fetus from xenobiotic exposure. Identifying regulators of placental BCRP expression is critical as downregulation of BCRP expression may increase fetal exposure to drugs and chemicals. We hypothesize that the nuclear receptor peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) regulates BCRP expression in the placenta. To test this hypothesis, human BeWo placental choriocarcinoma cells were cultured with the PPAR $\gamma$  agonist rosiglitazone (1-60  $\mu$ M), or, the PPAR $\gamma$  antagonist T0070907 (10  $\mu$ M) for 24 hrs. mRNA and protein expression of BCRP and markers of placental trophoblast syncytialization (syncytin and hCG) were quantified using qPCR and western blot analysis, respectively. Compared to vehicle-treated cells, BCRP mRNA expression increased dose-dependently with PPAR $\gamma$  agonist treatment up to 61% at 15  $\mu$ M. Similar changes in protein expression were observed. Conversely, antagonism of PPAR $\gamma$  signaling decreased BCRP mRNA and protein levels by 38%. In response to modulation of PPAR $\gamma$  signaling, changes in BCRP mRNA and protein mirrored the regulation of syncytin and hCG mRNAs. Our results suggest that the PPAR $\gamma$  receptor regulates BCRP expression in the placenta, which may be important in understanding mechanisms that protect the fetus from xenobiotic exposure during development. Supported by R01 ES020522, R25 ES020721, and R21 DK093903.

Originally was presented at Mid-Atlantic Society of Toxicology (MASOT) Annual Meeting Oct 16, 2014



**146<sup>TH</sup> Annual Meeting & Convention**  
Harrah's Resort & Casino  
**October 2016**

## Practice Spotlight:

### Disaster Medical Assistance Team (DMAT)

I am a 1963 PCP&S (University of the Sciences at Philadelphia) graduate and began the practice of pharmacy in a more traditional route as a retail pharmacist. I married my wife, Loretta, who is also a pharmacist; we eventually owned and subsequently sold our pharmacy. My practice expanded into the realm of the military, where I became the Chief Pharmacy Officer of the 108th Combat Support Hospital of the Pennsylvania Army National Guard, and also the Nuclear, Biological, Chemical Defense Officer which was my entree in to the world of HAZMAT.

During that time, I became a supervisor at Lyons Veterans Affairs (VA) Hospital which happened to be the home of the fledgling NJ-1 Disaster Medical Assistance Team (DMAT). At that time, DMAT was under the United States Public Health Service (USPHS). When Hurricane Hugo hit in 1989, I heard there was a need for pharmacists and learned about the NJ-1 DMAT at the same time. I inquired about it and finally joined in the early 90's.

In May of 1999, an influx of Kosovo refugees, escaping persecution in their country, arrived at Fort Dix, New Jersey. Elements of NJ-1 DMAT were deployed and I was included. I worked with a few other DMAT pharmacists from other states as well as USPHS pharmacists. Lacking the simple tools of the trade such as scales, spatulas, powder papers, USP's and NF's, I found myself making children's tuberculosis (TB) cocktails using clean white paper, a hammer, and a knife edge. I pulverized tablets of INH and PBZ; with a knife edge, I subdivided the powders into the approximate doses required by the physicians' orders. Of course, we were also filling regular prescriptions, using medications supplied by a Public Health Hospital. This was a two week deployment which was quite different from the military, VA, and retail pharmacy practices to which I had grown accustomed.

On Tuesday morning in September 2001, while working in my office at the Lyons VA Medical Center, someone came to tell me to come quickly to the waiting room. I arrived in time to see the second tower of the World Trade Center hit by the second plane. As it crumbled down, I just knew the DMAT would be called; I got permission to leave. About two hours later, I was on my way to the DMAT assembly point at Fort Dix. Meeting up with NJ-1 DMAT and the NJ Naval Militia, we received orders; loaded our equipment, including our 72 hour drug cache; and convoyed out. We drove through the closed Holland Tunnel led by a New York City garbage truck. After passing through armed check points, we arrived at Chelsea Pier, which is just a few blocks from Ground Zero. There, we joined with responders and other volunteers by the hundreds.

The City of New York, known for its EMS, Fire and Police departments, were handling the response at that time; they were not ready to utilize all these hands. So, the responding teams were staged at the then Stewart Air Force Base, in Newburgh, NY. NJ-1 DMAT met about 600 of our "closest friends" and were housed in the hangar of a CSA, a very large facility indeed. As the response proceeded on the ground, the requirement for pharmacists became evident. As the only two pharmacists in the house, my partner, Harold Bobrow, and I were sent to work around Ground Zero.

The Strategic National Stockpile that had been deployed was intended for survivors, but unfortunately there were too few survivors. What was needed were supplies for responders working on the pile – a very dangerous, unstable pile of noxious fumes, steel, concrete and subsurface fires. Respiratory problems, trips, falls, heat exhaustion, sprains, strains, and fractures were some of the problems being faced. Harold and I took action at every pharmacy in downtown New York with a government credit card, clearing shelves of inhalation products, eye solutions, and anything else that looked usable. We delivered our "booty" to each of the 5 treatment facilities surrounding the pile. To complete the requisition process, we initiated the Vendor Managed Inventory (VMI), ordering large quantities of supplies direct from the manufacturers. These supplies were flown in on a FedEx aircraft, the only airline permitted to fly by the federal government, since the declaration of a Disaster and a Terror Attack.

We also delivered supplies to the hospital ship Mercy, which happened to be docked at Pier 93. It was serving the more severely wounded responders, both human and canine. I recall passing through at least two heavily armed check points to get to the ship. Following large trucks loaded with debris on the way to the Fresh Kills site where teams of pathologists who were waiting to sort through for human remains. It was very emotional. We knew we were looking at the remains of probably hundreds of mothers, fathers, sons, daughters, and family members of our neighbors and fellow citizens. Harold and I were finally relieved after two weeks by a pharmacist of the USPHS.

On 25 August 2005, Hurricane Katrina struck the Gulf Coast with terrifying consequences, laying waste a great portion of Gulf Coast cities and flattening 150 miles of coastline. The sad part was that state and municipal governments failed to enact any kind of response for the safety of their citizens. In retrospect, there seems to have been no plan in place to maintain an infrastructure in case of a disaster.

NJ-1 DMAT, along with many other DMAT's and other federal response teams, was activated. We were sent to Keesler Air Force Base in Biloxi, MS. From there, we were first sent to Garden Park Hospital in Gulfport; its first floor was flooded, including the Admitting and the OR departments. We set our tentage outside the hospital entrance and served as Triage, Admitting, and OR for about a week, until the hospital regained its capability.

From there, we were deployed to the Biloxi High School, which the Mississippi Militia occupied. They had to be expelled, which was only accomplished by overwhelming Federal force. However the room, which served as an armory with much of their weaponry, was on lock down. The high school served as a clinic serving everyone, including special-needs patients. Harold and I took over the pharmacy, which occupied the computer room and was initially operated by the California DMAT. The clinic was staffed by local medical personnel displaced from their own practices, deployed teams, and medics from the adjacent counties. Medications supplied by DMAT team caches were by no means sufficient for the demand. We were blessed by the fact that the

doctors' offices, that were flooded, were prepared. Their staff had bagged their samples and delivered them to us in garbage bags. We sorted them out, with the help of a first-rate pharmacy technician from the California team, and placed them by category around the room.

Without medical records, we had to dispense meds by diagnosis and patient recall. Orders came to us via the medical staff seeing the patients, and Harold and I had to come up with what we hoped would be the appropriate medication sufficient for a week. This continued for about three or four days until the local Walmart opened and agreed to allow FEMA to pay for a 30-day supply for each patient. Most were refills of what we had previously dispensed. We also sent strike teams to visit surrounding medical sites, which were operated mostly by faith-based organizations. We shared needed medications as well as helped treat some of their patients.

The experience of witnessing the human suffering that occurs when there is no plan, seeing buses parked in their lots totally useless, and hearing about the evacuation fiasco at the Louisiana Superdome, returned to me at a meeting of the Bioterrorism Task Force of Warren County of which I was a member. I became one of several people advocating for the start-up of the Medical Reserve Corps, and ultimately became a co-coordinator of the Warren County unit.

Fast forward to 12 January 2010. A devastating 7.0 earthquake hit with an epicenter 16 miles west of Port-au-Prince, Haiti's capital. Death estimates ranged anywhere from 100,000 to over 200,000, though some government estimates were higher. President Obama called for massive response from the United States, which included the National Disaster Medical System (NDMS), now under the Assistant Secretary for Preparedness and Response (ASPR) and the Department of Health and Human Services (HHS). Several DMATs were called up, NJ-1 DMAT being among the first. This was to be the first Off-Continental US (OCONUS) deployment for any DMAT. We first went to Atlanta, Georgia for shots and briefings. Of course, this did not prepare us for what actually happened on the ground.

Arriving at the Port-au-Prince airport, we found it was a single strip runway with a building damaged by the quake. Large military and commercial aircrafts were pouring onto a runway designed for, maybe, a 30th of the amount of traffic causing immense tie-ups and delays of personnel and equipment arriving from many countries at once. The whole air traffic control was being handled out of a small tent expertly manned by US Air Force personnel. Finally getting a ride to the US Embassy, we found ourselves literally climbing up and into a white painted refuse truck, which is normally used for hauling the deceased to mass graves. At the embassy, we slept on the damp, worm-inhabited lawn. We were denied the use of the embassy building by the ambassador, who had no idea who we were or what our mission was. Of course many of us snuck in anyway. Finally, cots, tents, water, and food arrived so life on the green became a bit more bearable.

Being an OCONUS deployment meant we were under the State Department. However, it took about three days for the State Department to get its act together. Our orders finally got issued;

our team and CA-1 DMAT were sent to the Petionville Country Club to set up our hospital. We were fortunate to be embedded with 82nd Airborne forces that were already there. Our Base of Operation (BOO) tentage was set up on the green of the first hole of the golf course since this provided the space for the hospital and the landing zone for the steady flow of choppers bringing food and water for the residents of the tent cities camped below. The only access to our facility was a goat trail up a fairly steep hill which could only be navigated in daylight; however, folks needing care did manage, many with the help of their family members.

My pharmacy was initially set up poolside with cases and pallets spread out for easy access, but this proved to be a poor choice when the big Navy Super Stallion helos flew over. There were scattered pharmaceuticals all over and damage to some of the DMAT tentage as well as the 82nd's. It wasn't long before the flight paths were changed; my pharmacy was re-established in the poolside bar. It was great for security, and a little tight to work in, but we managed. I had a pharmacist from Pennsylvania and one from the California team, and we worked fine together.

During the three week deployment, we saw nearly 6000 patients and welcomed quite a few babies into the world. We sent medical strike teams into the tent cities and gave what care we could. Initially, it was "treat and street" as there were no beds available. US Coast Guard Haiti was a small station with a small cutter. They would fly medics out to the cutter, boat the patients to the cutter, treat them and send them back to shore by boat. Fuel for the chopper was limited.

Beds became available when the University Hospital reopened partially staffed by the Georgia DMAT, and the air craft carrier, Carl Vinson, arrived and made its medical capability available. Israel opened a complete Surgical Hospital with other nations starting medical facilities as well. Haiti was a HAMAT situation, with no sanitation, no potable water, although Haitian Rum is outstanding. Over-crowding was a problem as well, so said the CDC personnel assigned to the area. We did what surgery we could without X-rays, although some patients brought their own. Anesthesia was in short supply, but bite sticks were not; our patients appreciated anything we could do for them.

We did a lot of debridement, set broken bones, treated crush injuries and even created rape kits. We dispensed lots of pediatric antibiotics, and lots of GI meds. There was plenty of Pepto Bismol available. We supplied lots of baby food too!

I have enjoyed being part of NJ-1 DMAT and have moved up into the Logistics aspect of response. I feel I have had a hand in helping to create a more resilient, safer world. The practice of Disaster Pharmacy differs with every event, and you have no clue until your boots are on the ground. Flexibility is the key.

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# New Therapeutic Options for Diarrhea Predominant Irritable Bowel Syndrome (IBS-D)

By: Janine S. Douglas, Pharm.D., BCPS; Tanya Riley, Pharm.D., BCPS; April Robinson, Pharm.D., BCPS

## **Introduction**

Irritable bowel syndrome (IBS) is a chronic, functional bowel disorder characterized by abdominal pain, bloating, diarrhea, or constipation that affects 12% of the US population. It is associated with diminished quality of life and is twice as prevalent in women as compared to men. IBS may present as altered stool consistency: diarrhea predominant (IBS-D), constipation predominant (IBS-C), or mixed pattern (IBS-M), alternating between constipation and diarrhea.<sup>1</sup> Patients with IBS have unstable bowel patterns and up to 75% of IBS sufferers may change IBS subtypes and 29% may cycle between IBS-D and IBS-C over the course of 1-year.<sup>2</sup>

The etiology of IBS is varied and not well understood. Proposed mechanisms thought to cause IBS include disturbances in intestinal bacterial colonization, small intestine bacterial overgrowth, dietary factors, and abnormal perception of visceral pain.<sup>2</sup> Also, the nervous system innervating the gastrointestinal tract contains a large percentage of serotonin receptors (5HT) which appear to play a role in the abdominal pain and discomfort experienced in IBS patients.<sup>3</sup>

IBS is diagnosed using the Rome III criteria which states “the reoccurrence of abdominal pain or discomfort for 3 or more days per month in the last 3 months that is associated with one or more of the following: improvement with defecation, onset associated with a change in frequency of stools, and onset associated with a change in the appearance of the stools.”<sup>4</sup> Treatment options for IBS differ based on management of the predominating symptom, diarrhea or constipation.<sup>1,2</sup> Current therapeutic options for IBS-D include increasing dietary fiber, managing stress, and the use of antidepressants, antidiarrheals, antispasmodics, and alosetron.<sup>1,2</sup> Alosetron, a 5HT<sub>3</sub> antagonist, is indicated for the relief of abdominal pain, bloating, and diarrhea associated with IBS-D in women. However, its use is limited due to increased risk of fatal ischemic colitis and severe constipation.<sup>5</sup> New treatment options for IBS-D focus on targeting serotonin antagonist subtypes, 5HT<sub>3</sub> and 5HT<sub>4</sub>, mechanisms to decrease abnormal visceral pain sensitivity, and modulating gut bacteria to alleviate global symptoms.<sup>3</sup>

The United States Food and Drug Administration (FDA) has recently approved two drugs, eluxadoline and rifaximin, for the treatment of IBS-D. The aim of this review is to provide an overview of new therapeutic options for IBS-D including pharmacology, safety, and efficacy.

## **Eluxadoline**

Eluxadoline is a combination mu-opioid receptor agonist and delta opioid receptor antagonist indicated for the treatment of IBS-D in adult men and women.<sup>6</sup> It is available as a 75 mg and 100 mg oral tablet administered twice daily with food. The 75 mg oral tablet dose is recommended in patients who do not have a gallbladder, are unable to tolerate the 100 mg eluxadoline dose, are taking concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment. Eluxadoline is contraindicated in patients with known or suspected biliary duct obstruction, sphincter of Oddi

disease or dysfunction, history of pancreatitis, pancreatic structural disease including known or suspected pancreatic duct obstruction, severe hepatic impairment, known or suspected gastrointestinal obstruction, severe constipation or sequelae from constipation, alcohol addiction, alcoholism, and alcohol abuse. Also, patients who consume more than three alcoholic beverages a day should not take this medication due to increased risk of pancreatitis.<sup>6</sup>

In animal studies, eluxadoline demonstrated a localized effect on opioid receptors in the gut by normalizing fecal output without completely blocking gastrointestinal movement.<sup>6,7</sup>

When administered orally, eluxadoline has very low bioavailability and close to linear pharmacokinetics with no accumulation seen with constant twice daily dosing.<sup>6,7</sup> Excretion of eluxadoline was evaluated by administering a single 300 mg dose of eluxadoline to healthy male subjects. Approximately 82% of the total radioactivity was recovered in the feces within 336 hours and less than 1% was recovered in the urine within 192 hours.<sup>6,8</sup>

Constipation was the most common adverse reaction observed in eluxadoline treated patients with about half of the events occurring within the first 2 weeks of therapy.<sup>6</sup> A phase II study reported constipation events occurring more frequently in patients within the 100mg eluxadoline therapy group. However, the events were mild and tolerable and did not result in patient discontinuation of medication.<sup>7</sup> Other common adverse reactions noted in more than 2% of patients were nausea, vomiting, and abdominal pain.<sup>6,7</sup>

A randomized, double-blind, placebo controlled phase II study evaluating benefits of eluxadoline therapy in adult patients with IBS-D assigned patients to receive placebo, eluxadoline 5 mg, 25 mg, 100 mg, and 200 mg doses twice daily for 12 weeks. Daily responders, based on FDA recommendations, were defined as patients who experienced a 30% or greater decrease in daily worst abdominal pain measurements (WAP) from baseline, a daily Bristol Stool Scale score of less than 5, or reported no bowel movement within the study period.<sup>7</sup> Post hoc analyses endpoints results reported response rates significantly higher in patients taking eluxadoline 100 mg ( $p=0.002$ ) and 200 mg ( $p=0.002$ ) doses compared to placebo. A statistically significant higher stool consistency response was observed in patients taking 200 mg eluxadoline ( $p=0.013$ ) when compared to placebo, with a positive trend toward statistical significance ( $p=0.059$ ) in patients taking 100 mg eluxadoline. Also, there was a significantly greater number of patients in the 100 mg eluxadoline arm ( $p=0.045$ ) who met the WAP measurement criteria compared to the placebo arm.<sup>7</sup>

Two randomized, double blind, multi-center phase 3 clinical studies evaluated safety and efficacy of eluxadoline therapy over 26 weeks in patients who were administered twice daily doses of 100 mg eluxadoline, 75 mg eluxadoline, and placebo. Study data was collected via patient electronic daily dairies. The primary composite endpoints were the number of patients who met

simultaneous improvement in daily worst abdominal pain score by 30% or greater compared to weekly baseline averages and a decrease in the Bristol stool scale to less than 5 for at least 50% of the time during a 12 week period. Also, a response day included improvement in daily worst abdominal pain in the absence of concurrent bowel movement. Study results reported higher rates of stool consistency responses observed over 12 weeks of eluxadoline therapy when compared to placebo. Both phase 3 studies composite endpoints reported statistically higher response rates ( $p<0.001$ ,  $p=0.004$ ) over 12 weeks and ( $p\leq0.001$ ,  $p<0.001$ ) over 26 weeks respectively in patients who received eluxadoline 100 mg therapy. When compared to placebo, both the 75 mg and 100 mg doses of eluxadoline demonstrated sustained efficacy throughout the treatment period.<sup>6,9</sup>

### **Rifaximin**

Rifaximin, a non-systemic antibiotic derivative of rifamycin, indicated for use in travelers' diarrhea and hepatic encephalopathy was investigated for use in the treatment of IBS-D. The rationale for use was its efficacy in the treatment of enteric pathogens and potentially modulating gut bacteria which may have a role in the pathogenesis of IBS-D. Rifaximin has minimal systemic absorption and a low risk of bacterial resistance which makes it suitable for use in IBS-D. The dose of rifaximin approved for IBS-D is 550 mg given three times a day by mouth for 14 days and may be repeated for up to 2 additional courses. Rifaximin can be taken without regard to food and is metabolized by P-glycoprotein 3A4. The major drug interaction reported by the manufacturer is with cyclosporine, which can increase the exposure of rifaximin. The half-life of rifaximin ranges from 5.6 to 6 hours in healthy patients versus IBS patients respectively and is excreted as unchanged drug in the feces (96.62%).<sup>10</sup>

Meyrat and colleagues evaluated the efficacy of rifaximin in 150 IBS patients (81% IBS-D). Four weeks prior to receiving a 14 day course of rifaximin patients were given a lactulose hydrogen breath test (LGBT) to detect changes in intestinal bacterial growth as many IBS patients are positive for small intestinal bacterial overgrowth (SIBO). Patients were then given rifaximin 200 mg four times per day if they tested positive. LGBT results were negative after treatment in 55 of the 64 previously positive patients (86%), and statistically significant improvements were seen in all symptom categories (bloating, diarrhea, flatulence, and abdominal pain) as well as overall wellbeing.<sup>11</sup> Another study of over 300 IBS patients in Romania focused on the prevalence of SIBO with IBS and the response to treatment with rifaximin.<sup>12</sup> Patients who tested positive for SIBO (46% of IBS patients), via the glucose hydrogen breath test (GHBT), were treated with 1200 mg per day (400 mg three times a day) of rifaximin for seven days, then retested for SIBO. After treatment with rifaximin, the GHBT was normal in 85.5% of patients. Additionally, 46.6% had complete improvement of symptoms ( $p=0.0005$ ) and 31.4% had a partial improvement ( $p=0.7$ ).<sup>12</sup>

Two multicenter, phase 3, double blind, placebo controlled studies, TARGET 1 and TARGET 2, evaluated the efficacy and sustainability of oral rifaximin in greater than 1200 patients with IBS without constipation. Patients were randomly assigned to receive placebo or rifaximin 550 mg three times daily for 2 weeks. After discontinuation of therapy, patients were evaluated for an

additional 10 weeks as follow-up. For both studies, the primary endpoint was the proportion of patients who experienced adequate relief of global IBS symptoms for at least 2 weeks during weeks 3 through 6 of the study. A key secondary endpoint evaluated the proportion of patients who had adequate relief of IBS related bloating during the primary evaluation period.<sup>13</sup>

Significantly more patients in the rifaximin group met the primary endpoint of adequate relief of global IBS symptoms when compared to placebo in both the TARGET 1 (40.8% vs 31.2%,  $p=0.01$ ) and TARGET 2 studies (40.6% vs 32.2%,  $p=0.03$ ). Rifaximin patients meeting the primary endpoint experienced relief within the first month of the study, with sustained relief seen throughout the study period (TARGET 1  $p=0.05$ ; TARGET 2  $p=0.005$ ). Regarding the secondary endpoint, a greater number of patients in the rifaximin group achieved adequate relief of IBS related bloating than placebo (TARGET 1 39.5% vs 28.7%,  $p=0.005$ ; TARGET 2 41% vs 31.9%,  $p=0.02$ ). Other results of the TARGET 1 study suggest that more patients in the rifaximin group achieved IBS related bloating relief within the first month of the study with continued relief throughout the first 2 months. In the TARGET 2 study, relief of IBS related bloating was observed throughout the entire 3 month study period (TARGET 1  $p=0.10$ ; TARGET 2  $p=0.001$ ). Reported adverse events were similar for both the rifaximin and placebo groups with no patients experiencing death, *Clostridium difficile* associated diarrhea, or ischemic colitis.<sup>13</sup>

A recent randomized, placebo controlled study (TARGET 3) evaluated the efficacy and safety of repeat treatment with rifaximin in more than 600 patients with IBS-D. Studied patients were previous responders to rifaximin therapy who developed recurrent symptoms during the 18 week observation period. The primary endpoint was the percentage of patients who experienced improvement in both abdominal pain (greater than or equal to 30% decrease from baseline mean weekly pain score) and stool consistency (greater than or equal to 50% decrease from baseline in number of days per week with bowel movements) at least 2 weeks per month. Results reported similar efficacy in rifaximin retreated patients compared to rifaximin naïve patients. Response rates were 33% compared to 25% for placebo ( $p=0.02$ ). Of note, retreated patients experienced less severe symptoms than before initial rifaximin therapy. As a result, retreatment of previous responders may be appropriate.<sup>14</sup>

### **Conclusion**

With a reported 12% of the US population affected by IBS, the addition of two new treatment alternatives for IBS-D, eluxadoline and rifaximin, can benefit patients by relieving symptoms and improving their quality of life. Eluxadoline is a novel, mu receptor agonist and delta opioid receptor antagonist, which is efficacious in relieving symptoms of abdominal discomfort and improving stool consistency. The most common adverse effect experienced with eluxadoline is constipation but it did not result in frequent discontinuation of the medication. Rifaximin, a non-systemically absorbable rifamycin derived antibiotic active against enteric pathogens, has demonstrated efficacy in alleviating the symptoms associated with IBS-D. The recommended treatment course is 14 days of therapy for up to 2 additional courses where patients who previously did not respond may have favorable responses with additional treatment courses. The FDA approval of eluxadoline and rifaximin has added additional treatment options for bloating, abdominal discomfort, improvement in stool consistency, and global IBS symptoms for IBS-D sufferers.

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UNITED STATES POSTAL SERVICE® (All Periodicals Publications Except Requester Publications)									
1. Publication Title	2. Publication Number	3. Filing Date							
The New Jersey Journal of Pharmacy	0 0 2 B 5 7 7 3	Nov. 30, 2015							
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price							
Quarterly	4	\$50 US							
7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4?)	C/o Barry								
760 Alexander Road, Princeton, NJ 08543	Telephone (Include area code) 609-275-4246								
8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer)									
same as above									
9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)									
Publisher (Name and complete mailing address)									
Eliza M. Barry NJPhA 760 Alexander Rd., Princeton, NJ 08543									
Editor (Name and complete mailing address)									
Maria Leibfried NJPhA 760 Alexander Rd., Princeton, NJ 08543									
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N/A									
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Full Name	Complete Mailing Address								
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11. Known Bondholders, Mortgagors, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box	X. None								
Full Name	Complete Mailing Address								
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12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)									
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:									
<input checked="" type="checkbox"/> Has Not Changed During Preceding 12 Months									
<input checked="" type="checkbox"/> Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement)									

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13. Publication Title	14. Issue Date for Circulation Data Below	
New Jersey Journal of Pharmacy	Fall issue Dec. 2015	
15. Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	
Members & subscriptions	No. Copies of Single Issue Published Nearest to Filing Date	
a. Total Number of Copies (Net press run)	381 350	
(1) Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	263 166	
b. Paid Circulation (By Mail Outside the Mail)	(2) Mailed In-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	13 5
(3) Paid Distribution Outside the Mail including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS®		
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c. Total Paid Distribution [Sum of 15(b), (2), (3), and (4)]	276 171	
d. Free or Nominal Rate Distribution (By Mail Outside the Mail)	(1) Free or Nominal Rate Outside-County Copies included on PS Form 3541	
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(4) Free or Nominal Rate Distribution Outside the Mail (Carriers or other means)	100 174	
e. Total Free or Nominal Rate Distribution (Sum of 15d (1), (2), (3) and (4))	100 174	
f. Total Distribution (Sum of 15c and 15e)	376 345	
g. Copies not Distributed (See Instructions to Publishers #4 (page #3))	5 5	
h. Total (Sum of 15f and g)	381 350	
i. Percent Paid (15b divided by 15f times 100)	73.40 49.57	
16. Electronic Copy Circulation	Average No. Copies Each Issue During Preceding 12 Months	
a. Paid Electronic Copies	No. Copies of Single Issue Published Nearest to Filing Date	
b. Total Paid Print Copies (Line 15c) + Paid Electronic Copies (Line 16a)		
c. Total Print Distribution (Line 15f) + Paid Electronic Copies (Line 16a)		
d. Percent Paid (Both Print & Electronic Copies) (15b divided by 15c > 100)		

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17. Publication of Statement of Ownership

If the publication is a general publication, publication of this statement is required. Will be printed

Publication not required

in the Fall 2015 issue of this publication.

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*Eliza M. Barry* Date 11/30/15

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145<sup>th</sup> Annual Meeting and Convention  
October 16, 2015 – October 18, 2015

# *Congratulations 2015 Awards Recipients*



**MORTAR AND PESTLE AWARD**  
Michael Alvatroni, PhD



**BOWL OF HYGEIA AWARD**  
Edward McGinley, MBA, RPh



**FREDERICK B. KILMER AWARD**  
Carmela Silvestri, PharmD, CCP, FASCP



**NCPA PHARMACY LEADERSHIP AWARD**  
Ruth A. Marietta, RPh, CCP



**WILLIAM H. MCNEILL AWARD**  
Edward Rucki, RPh, CCP



**NASPA EXCELLENCE IN INNOVATION AWARD**  
Chester Lau, RPh, MS



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