Methadone analgesia in the critically ill☆

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ABSTRACT

Purpose: Methadone is increasingly used as an analgesic or a bridge to weaning other analgesics and sedatives in critically ill patients. This review discusses the pharmacology of methadone, summarizes available evidence for its use in the intensive care unit setting, and makes suggestions for appropriate use and monitoring.

Materials/methods: Articles evaluating the efficacy, safety, and pharmacology of methadone were identified from a PubMed search through June 2015. References from selected articles were reviewed for additional material. Experimental and observational English-language studies that focused on the efficacy, safety, and pharmacology of methadone in critically-ill adults and children were selected.

Results: Methadone is a synthetic opioid analgesic with potential advantages over other commonly used opioids. Limited evidence from critically ill pediatric, adult, and burn populations suggests that methadone protocols may expedite weaning opiate infusions, decrease the length of mechanical ventilation, and reduce the incidence of negative outcomes such as opiate withdrawal, delirium, and over-sedation.

Conclusions: Data from current literature supports a role for methadone analgesia in weaning opiates and potentially reducing the duration of mechanical ventilation in critically ill patients. More studies are needed to confirm these benefits and determine criteria for patient selection.

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1. Introduction

Methadone is increasingly being used for pain management in the intensive care unit (ICU) [1–6]. This expanding use of methadone is partially driven by a growing awareness that pain is often under-recognized and under-treated in critically ill patients [7,8]. An increased focus on pain management has been encouraged by The Joint Commission on Accreditation of Healthcare Organizations, the American Pain Society, and Centers for Medicare/Medicaid Services [9]. In addition to unnecessary suffering, under-treated pain may contribute to post-traumatic stress disorder and increased metabolic oxygen consumption during the stress response of critical injury [10,11]. Pain-related agitation also makes routine nursing care difficult and contributes to patient-ventilator dyssynchrony [12].

Although agents such as benzodiazepines and propofol have traditionally been used for sedation in the ICU, evidence is accumulating that these drugs may increase the risk of delirium, duration of mechanical ventilation, and ICU length of stay [12–16]. Such concerns are highlighted in the 2013 clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU sponsored by the Society of Critical Care Medicine. These guidelines hope to improve patient outcomes by endorsing the concept of “analgo-sedation,” a focus on optimizing analgesia to decrease the need for sedatives [13,14,15].

Methadone is well suited for long-term analgesia in critically ill patients with prolonged opiate exposure [3]. However, its use by inexperienced prescribers can be dangerous [17]. Effective and safe use of methadone requires appropriate patient selection and monitoring based on methadone’s pharmacology, side-effect profile, and potential drug-interactions. Currently published literature guiding the use of methadone in critically ill patients is limited. This review will discuss the pharmacology of methadone, summarize available research in critically ill patients, make suggestions for appropriate use, and highlight opportunities for further study.

2. Methods

A search of the PubMed database was completed to identify relevant articles published through June 2015 utilizing the following MeSH terms: methadone, critically ill, analgesia, and intensive care. All abstracts and titles were screened to identify studies pertaining to the efficacy, safety, or pharmacology of methadone in critically ill patients. Reference lists were reviewed to identify additional relevant
publications. Non-human studies and non-English language publications were excluded. All identified articles in which methadone was used in critically ill patients were reviewed by the authors. Data was initially summarized by the first and senior authors (JLE, MRL) with subsequent review and revision by all authors.

3. Pharmacology of methadone

Methadone is an opioid analgesic with unique pharmacodynamic properties that differentiate it from other opioid analgesics. Its effects are centrally-mediated through agonism at the μ-opioid receptor, antagonism at the N-methyl-D-aspartate (NMDA) receptor, and inhibition of serotonin and norepinephrine reuptake [18,19]. While methadone’s μ-receptor agonism accounts for the majority of its analgesic effect, its antagonism at the NMDA receptor and inhibition of serotonin reuptake contribute additional anti-nociceptive effects beyond those of traditional opioids [17]. NMDA receptor antagonism may contribute additional benefits by increasing methadone’s effectiveness in the treatment of neuropathic pain and preventing maladaptive responses to acute pain that can progress to chronic pain through the remodeling of pain pathways [17,18].

The pharmacokinetic properties of methadone have been widely described, but the majority of this data was collected in healthy subjects or patients in opioid maintenance programs. Therefore, such data may not be representative of the critically ill population (Table 1). Methadone is commercial availability as an oral tablet, an oral solution, and an intravenous solution for injection. Methadone is highly lipophilic, allowing for rapid absorption and a long duration of action following oral administration [18]. The oral bioavailability of methadone has been reported between 70–80%, with time to peak plasma concentrations ranging from 2.5 to 4 hours following enteral administration [18,20–22]. Tube feeding is not known to alter the enteral absorption of methadone. Following intravenous administration, the time to peak plasma concentration is approximately 12 to 20 minutes [23].

Methadone’s terminal half-life ranges between 7 and 65 hours, with a large degree of inter-patient variability [23]. Based on the long half-life, methadone will not reach steady state for several days after initiation or dosage adjustments. Elimination of methadone into inactive metabolites occurs principally through hepatic metabolism by the cytochrome P450 enzyme-system [18,21]. The CYP3A4 and CYP2B6 enzymes are responsible for the majority of methadone metabolism [23,25]. Excretion occurs largely via the feces, while about 20% of the drug is excreted unchanged in the urine [25].

Methadone accumulation is seldom seen in the setting of renal and hepatic dysfunction [25]. In patients with severe chronic liver disease, methadone’s terminal half-life was prolonged without any observation of increased sedation [26]. This suggests that dosage adjustment is not necessary in patients who have chronic liver disease, although the frequency at which the dose is titrated upward may need to be decreased. [26] No specific recommendations exist regarding dosing adjustments for methadone in the setting of severe, acute hepatic impairment; decreased activity of the cytochrome P450 enzymes responsible for methadone metabolism should be expected [25]. Therefore, empiric methadone dose reduction in patients on existing methadone therapy, and lower initial doses should be considered in patients with severe, acute hepatic impairment. Renal impairment also has little impact on the pharmacokinetic profile of methadone. Methadone plasma concentrations do not increase significantly in anuric patients, as excretion in the feces is enhanced [27]. Therefore, dosage adjustment and slow upward titration is only be recommended in severe renal impairment [25]. As methadone is not removed by hemodialysis, dosage adjustments for renal replacement therapy are not necessary [27,28].

Methadone has several unique side effects in addition to the well-established adverse effects of the opiate class, such as sedation, respiratory depression, and constipation. Notably, these include QT interval prolongation and potential development of serotonin syndrome. Excessive sedation with methadone use is an avoidable problem usually caused by overly-rapid upward titration [18,23]. Methadone’s QT prolongation results from a delay in ventricular repolarization, and may place patients at risk for arrhythmias, particularly torsades de pointes [23,29]. Methadone’s weak inhibition of serotonin reuptake imparts the risk for serotonin syndrome. This is less likely when methadone is used alone, so concurrent use of other medications that impact serotonin concentrations should be minimized.

A significant concern for drug-drug interactions exists since methadone’s metabolism relies on the cytochrome P450 enzyme-system [25]. Plasma concentrations of methadone can be increased by inhibitors of cytochrome P450, including azole antifungals, macrolide antibiotics, diltiazem, and verapamil [30]. Case reports of over-sedation and QT prolongation have been documented when these medications are used concurrently with methadone [30]. Interactions with inducers of the cytochrome P450 enzyme-system can also occur. In a case series of chronic methadone users, induction of methadone metabolism by rifampin resulted in severe withdrawal symptoms [31]. Similar reactions would likely occur with other well-known cytochrome P450 inducers. Although the clinical significance of all potential drug-drug interactions have not been fully evaluated [25], commonly used medications that may interact with methadone are summarized in Table 2.

4. Use of methadone in critically ill populations

While non-opioid adjuncts such as non-steroidal anti-inflammatory drugs, dexmedetomidine, and ketamine may help supplement analgesia, opiates remain the backbone of pain management in critically ill patients [32]. Opiate choice often depends on pharmacologic principles, institutional preference, or provider familiarity. No clear guidelines for opiate selection are currently available and few comparative trials have been performed in critically ill patients [12]. When critically ill patients with severe traumatic or burn pain require escalating doses of opiates and sedatives, intermittent dosing may prove inadequate, and continuous opiate infusions are often initiated [33]. After clinical recovery, weaning these infusions to facilitate extubation often presents a challenge due to the risk of opiate withdrawal. Higher opiate doses and longer durations of exposure increase this risk and may prolong the need for mechanical ventilation [34]. Many properties of methadone make it well suited for treating patients with severe pain, prolonged opiate exposure, and high opiate requirements [17,35].

Two early case series evaluated the utility of methadone for treating acute pain in critically ill pediatric burn patients. In 1989 Concilus et al. described the successful use of continuous methadone infusions in 17 pediatric patients with severe burn injuries [36]. These patients experienced significant pain relief with methadone, while maintaining hemodynamic stability. Several years later, Williams et al. described the successful “restoration” of sedation and analgesia with intravenous methadone in two burned pediatric patients who had rapidly escalating morphine requirements [6]. After methadone initiation, morphine was discontinued and administration of other sedative adjuncts such as

### Table 1

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>70–80%¹</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>85–90%</td>
</tr>
<tr>
<td>Half-life</td>
<td>7–65 hours¹</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>3.6 L/kg</td>
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<tr>
<td>Elimination</td>
<td>4–6 L/hour</td>
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¹ Large interpatient variability reported.
midazolam, ketamine, barbiturates, and chloral hydrate was greatly reduced. Notably, the dose of methadone used to achieve effective analgesia was significantly less than the equianalgesic dose of morphine previously required. Attempts to identify the optimal methadone dose to facilitate weaning of continuous opiate infusions in critically ill children have yielded conflicting results. Siddappa et al. retrospectively evaluated 30 pediatric ICU patients transitioned to methadone after being maintained on fentanyl infusion for more than 7 days [37]. A conversion factor of 3 times the daily fentanyl dose in milligrams was used to determine the daily dose of methadone in milligrams. Methadone was initially administered in divided intravenous doses, followed by oral dosing after 48 hours. Fentanyl infusions were discontinued after 24 hours. Patients who received less than 80% of the calculated methadone dose were more likely to exhibit signs of withdrawal than those who received at least 80% of the calculated dose. Conversely, another study did not detect a difference in withdrawal symptoms when comparing higher and lower dose methadone tapers in pediatric patients [35]. In the latter study, patients who received higher opiate doses or had longer opiate exposure prior to initiation of the methadone taper were at increased risk for withdrawal, regardless of the methadone regimen used (higher vs. lower dose). This discrepancy highlights the complexity of selecting a suitable starting dose for methadone. Multiple confounding factors, such as mechanisms of tolerance, volumes of distribution, variable enteric absorption, and genetic variability may play a role determining methadone requirements [17,35].

The optimal time frame for weaning off opiate infusions after starting methadone has also been looked at in pediatric ICU patients. In one small study, implementation of a protocol to guide weaning of opiate infusions after initiation of oral methadone decreased the median weaning time from 20 days to 9 days [5]. Another prospective study of 37 pediatric ICU patients who were exposed to at least five days of opiate infusion found no difference in withdrawal symptoms between a 5 day and 10 day methadone protocol [34]. Although these studies were unable to establish a gold standard dose or time frame for methadone weaning, they do suggest a benefit from a protocollized approach.

A limited body of literature exists regarding methadone’s utility in reducing the duration of opiate infusion and mechanical ventilation in critically ill adults. Al-Qadheeb et al. describe a successful protocol to convert adult ICU patients maintained on opiate infusions for longer than 72 hours to enteral methadone [38]. Initiation of methadone allowed discontinuation of continuous opioid infusion in 4.5 days compared to 7 days in the pre-protocol group. Although the duration of mechanical ventilation was not evaluated in this study, a subsequent randomized, blinded trial found a significant difference in time to extubation between patients assigned to an intravenous fentanyl taper and those assigned to an enteral methadone taper [2]. The time to extubation was 7 days and 4 days respectively, and no difference in the rate of opioid withdrawal was noted. Jones et al. retrospectively compared adult patients with burn injury who were started on methadone within 4 days of intubation to patients who were not [4]. Although there was some baseline disparity between groups (the methadone group was younger and had a higher rate of substance abuse), patients started on methadone early experienced more ventilator-free days during their ICU stay (16.5 ventilator-free days vs. 11.5 in the control group). Despite similar usage of benzodiazepines and other opiates between the two groups, the methadone group had a significantly lower percentage of Richmond Agitation and Sedation Scale (RASS) scores that indicated oversedation compared to the control group (11.3 vs. 35.5%). Another retrospective review of critically ill adult burn patients focusing on risk factors for delirium, observed that the use of methadone was associated with a lower risk of delirium (OR 0.7 [95% CI 0.5–0.9], P = .02) [38]. Few studies have reported safety data for methadone in critically ill patients. Jones et al. reported a single patient with a QTc interval above 480 milliseconds (msec) among those who received methadone and had an electrocardiogram (ECG) available for assessment. Unfortunately, only 56% of the total cohort had ECG data [4]. Al-Qadheeb et al. reported no difference in the incidence of QT prolongation (defined as QTc interval >500 msec or change by 60 msec from admission) between the methadone and the control group (45% vs. 50%, P = .79) [38]. Depending on the definition of QTc prolongation applied, the reported incidence of QTc prolongation in the non-critically ill population receiving methadone treatment ranges from 0.3 to 83%, with few patients developing torsades de pointes [39–44]. While the relationship between daily methadone dose and QT prolongation remains controversial, it is fairly consistent that low-dose methadone (less than 100 mg/day) does not have an association with QTc prolongation [29,40–42,45]. A retrospective series of patients who were treated through methadone maintenance treatment centers and developed torsade de pointes found the mean daily methadone dose to be 397 mg per day [46]. This is a substantially higher dose than would be anticipated in the setting of critical illness. However, until further data is available regarding the safety of methadone in critically ill patients, practitioners should remain vigilant for adverse effects and consider risk factors that may predispose patients to excessive QT prolongation. This includes drug interactions, age greater than 65 years, female gender, concomitant QT prolonging medications (Table 2), electrolyte abnormalities, and structural heart disease [29,43].

<table>
<thead>
<tr>
<th>Cytochrome P450 Inhibitors:1</th>
<th>Cytochrome P450 Inducers:2</th>
<th>QT Prolongation:</th>
<th>Serotonin Syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoal Antifungals</td>
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<tr>
<td>Fluconazole</td>
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<tr>
<td>Voriconazole</td>
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<tr>
<td>Protease Inhibitors</td>
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<tr>
<td>Fluoroquinolones</td>
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<td>Ciprofloxacin</td>
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<td>Barbiturates</td>
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<td>Macrolides</td>
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<td>Erythromycin</td>
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<tr>
<td>Calcium Channel Blockers</td>
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<tr>
<td>Diltiazem</td>
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<tr>
<td>Verapamil</td>
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</tr>
<tr>
<td>SSRIs</td>
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<tr>
<td>Fluoxetine</td>
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<tr>
<td>Paroxetine</td>
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<td></td>
<td></td>
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<tr>
<td>Sertraline</td>
<td></td>
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<td></td>
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<tr>
<td>SSRIs: Serotonin Reuptake Inhibitors; SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Concurrent use may result in increased concentrations of methadone and development of adverse effects such as respiratory depression; consider starting at lower initial doses.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Concurrent use may result in decreased concentrations of methadone resulting in inadequate analgesic effect or withdrawal symptoms in patients on chronic methadone therapy.</td>
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</tr>
</tbody>
</table>
5. Recommendations for methadone use in the ICU

While the theoretical benefits of methadone analgesia in critical illness are compelling, there is presently limited evidence to guide patient selection, initial dosing, and treatment duration. Fortunately, many of the same principles that apply to methadone’s use in treating chronic pain and opioid withdrawal can be adapted to the ICU setting.

5.1. Patient selection

Initiation of methadone in patients requiring high doses of continuous analgesia and sedation may be considered to facilitate earlier weaning of sedation and to expedite liberation from mechanical ventilation. This may be especially useful in patients who have a history of chronic opioid usage or abuse. Burn patients particularly may benefit from methadone as it has been shown to provide good analgesia with less over-sedation and reduced days on mechanical ventilation in this population [4,36]. Due to its delayed onset and prolonged duration of action, methadone should not be used on an “as needed” basis for break-through pain or in patients who are not anticipated to require prolonged analgesia.

5.2. Initiation and titration

Because of incomplete cross tolerance with other opioids, it is common to experience unpredictable and widely variable patient responses to methadone initiation [23]. Therefore, methadone should be started at a relatively low dose, regardless of previous opioid exposure. Several different methadone conversion methods are reported in the literature (Table 3) [47–49]; however, when using methadone to facilitate weaning of continuous opioid infusion, an equianalgesic dose is not typically desired. We suggest initially dosing methadone every 8–12 hours and titrating no more frequently than every 3–5 days. Methadone concentrations will not reach steady state for a period of 3 to 7 days, so weaning other opioids is expected to take time as well. During this interval, patients may require rescue doses of quick acting opioids such as morphine, hydromorphone, fentanyl, or oxycodone. If continuous infusions or rescue doses are still required after a period of 3–5 days, an increase in methadone dose may be considered. Critically ill patients often have reduced or variable gastrointestinal absorption which could limit response to enteral methadone. In patients suspected of having impaired gastrointestinal absorption, methadone may be given intravenously, with conversion to oral methadone once enteral nutrition is tolerated. A conversion factor of 2:1 is recommended between oral and intravenous formulations [8]. The use of sublingual methadone has been evaluated in the palliative care setting, however this literature is limited by small patient numbers and focuses on the treatment of breakthrough pain [50,51]. With limited data to date regarding use of this route of administration in the critically ill population we would recommend limiting use of sublingual methadone to patients with lack of alternative options.

5.3. Discontinuation and weaning

The strategy for weaning and discontinuation of methadone will vary among patients based on current dose and duration of therapy. Abrupt discontinuation is not recommended as it can lead to the development of opiate withdrawal symptoms [52] Methadone can be weaned over a period of 5–10 days, decreasing the dose by 10–25% every 2–3 days. Patients with high or prolonged opiate exposure may require a prolonged wean over a period of weeks. Rescue doses of quick onset opioids should be available, and if initial attempts fail, the taper may need to be slowed. Prescribers can consider discontinuation once a total daily dose of less than 10–15 mg is reached.

5.4. Warnings and monitoring

Close monitoring for adverse effects and drug–drug interactions is required during methadone therapy. Patients should be carefully monitored for signs of respiratory depression, as methadone’s peak respiratory effects last longer than its peak analgesic effects [52]. This predisposes patients to the risk of overly rapid upward titration before steady state is reached. Methadone should be used cautiously in patients with a prolonged QT interval at baseline or risk factors for QT prolongation. It is important to note that most of the data regarding QT prolongation with methadone is from the non-critically ill population and may not be able to be extrapolated to the ICU. We recommend obtaining a 12 lead ECG prior to initiation of methadone in critically ill patients and at the time of any upward dosage titrations. Patients receiving concomitant serotonergic medications (Table 2) should be monitored for signs of serotonin syndrome throughout methadone therapy. Signs may include agitation, restlessness, hypertension, and diarrhea. Additionally, patients receiving methadone should be monitored for the development of opioid-induced constipation. Initiation of a bowel regimen may be necessary as with critically ill patients receiving other opioid medications.

6. Conclusions

Current data supports a role for methadone use in critically ill patients who require high doses and prolonged duration of analgesia and sedation. Methadone may help reduce overall sedation requirements, allow for more rapid discontinuation of continuous sedation and potentially decrease the time required to weaning mechanical ventilation. However, methadone should be used with caution in this population, and patients should be monitored for adverse effects such as delayed respiratory depression, QT prolongation, constipation and serotonin syndrome. Unfortunately, evidence is still limited, studies are small, and results are confined to specific groups of patients. Further

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**Table 3**

Methods of conversion to methadone from other opioid analgesics based on oral daily methadone equivalents

<table>
<thead>
<tr>
<th>Study</th>
<th>Equianalgesic Conversion to Oral Methadone</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ripamonti 1998</td>
<td>OME:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;90 mg/day</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td>90–300 mg/day</td>
<td>8:1</td>
</tr>
<tr>
<td></td>
<td>&gt;300 mg/day</td>
<td>12:1</td>
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<tr>
<td>De Conno 1996</td>
<td>OME:</td>
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</tr>
<tr>
<td></td>
<td>≤100 mg/day</td>
<td>5:1</td>
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<tr>
<td></td>
<td>101–300 mg/day</td>
<td>5:1</td>
</tr>
<tr>
<td></td>
<td>301–600 mg/day</td>
<td>10:1</td>
</tr>
<tr>
<td></td>
<td>601:800 mg/day</td>
<td>12:1</td>
</tr>
<tr>
<td></td>
<td>801–1000 mg/day</td>
<td>15:1</td>
</tr>
<tr>
<td></td>
<td>&gt;1000 mg/day</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Ratios are only valid for conversion to methadone and should not be used to convert from methadone to other opioids due to the risk of over-estimating the dosage requirements. OME, oral morphine equivalents.

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research is required to evaluate the safety and efficacy of methadone in critically ill patients.

References


[44] Roxane Laboratories I. Dolophine (Methadone Hydrochloride Tablets, USP) package insert[Columbus, OH]; 2015.