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executive editor letter

Fresh Beginnings
Jon Roth, MS, CAE

from the editor-in-chief

Message to the Readers
Karl Hess, PharmD, APP, FCPhA

original research

Evaluation of an Outpatient Pharmacy Clinical Services Program on Adherence and Fractures among Patients with Osteoporosis
Michele M. Spence, PhD; Abir F. Makarem, PharmD; Stacie L. Reyes, PharmD; Courtney Nguyen, BA

clinical problem-solving

Specialty Pharmaceuticals - Utilization Management
Craig S. Stern, RPh, PharmD, MBA, FASCP, FASHP, FICA, FLMI, FAMCP, FCPhA, CSP

law update

The End of Life Option Act: Important Considerations for Pharmacists as California Implements Physician Aid in Dying
Laura A. Petrillo, MD

special article

The End of Life Option Act - The Pharmacists Role
Tony J. Park, PharmD, JD

clinical practice capsule

DNA to Diagnosis to Treatment...
A Dependent Paradigm
Craig S. Stern, RPh, PharmD, MBA, FASCP, FASHP, FICA, FLMI, FAMCP, FCPhA, CSP

index

Advertisers

law update: continuing education

New Laws that Expand the Role of the Pharmacist in Patient Care
Fred G. Weissman, PharmD; Ettie Rosenberg, PharmD, JD

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Welcome to the new *Journal of Contemporary Pharmacy Practice (JCPhP)*! On behalf of the Editorial Committee, we are excited to showcase this fresh, new and exciting national scientific journal. The Editorial Committee, led by Editor-in-Chief Dr. Karl Hess, has been working hard to refine the publication to become one that will be sought after for its evidence-based manuscripts on the emerging contemporary modalities in pharmacy practice.

As the name indicates, the research papers you will read in this journal are targeted toward contemporary pharmacy practice. The goal is to highlight cutting-edge, practical, and applicable research centered around contemporary pharmacy practice. Authors and contributing scholars to the journal will be those who have a passion for advancing the practice of pharmacy through innovations in patient care delivery methods and clinical services delivered at the point of care in the pharmacy. These articles will also highlight the many important contributions being pursued within national and state pharmacy associations, schools and colleges of pharmacy, and among scientists and policymakers alike, all of whom are working to maximize the role of the pharmacist in patient care.

The *JCPhP* will be published quarterly in both digital and paper formats and will be available for pharmacists and other interested readers nationally. Additionally, *JCPhP* will be distributed to faculty and researchers at the schools/colleges of pharmacy with an invitation to contribute their works to the journal. The Editorial Committee believes that a broad and all-encompassing reach is important for gathering interesting and relevant articles that will contribute to the advancement of the profession. If you would like to submit a manuscript for publication, please visit jcphp.com, and you will be provided the instructions for submitting your paper.

We hope you enjoy the new *Journal of Contemporary Pharmacy Practice*! As always, we invite your feedback once you have had the opportunity peruse this edition. To learn more about the journal, go to jcphp.com or visit us on Facebook at facebook.com/jcpharmpractice/.

Happy reading!

Jon R. Roth, MS, CAE
Executive Editor
Dear Readers of the New Journal of Contemporary Pharmacy Practice,

As the editor-in-chief of the Journal of Contemporary Pharmacy Practice (JCPhP), I would like to take a moment to introduce you to our new Journal. As you may already be aware, the California Pharmacist Journal was rebranded to the JCPhP in an effort to provide greater national visibility for our authors and peer reviewers as well as those who serve the Journal and CPhA itself. This effort was a monumental undertaking directed by the Editorial Review Committee and took several years to complete. The Journal could not be what it is without the support and dedication of this group of individuals.

Like the California Pharmacist Journal was, JCPhP is a peer-reviewed publication and aims to publish relevant content for practicing pharmacists, academicians, student pharmacists, and pharmaceutical researchers. As such, JCPhP will inform, educate, and motivate readers to help them better serve their patients. We will continue to publish the Journal quarterly, both in print and online, under a continuous publication model. Those articles that are accepted for publication following peer review will be published online approximately one to two months in advance of the print version, thus allowing for greater visibility and exposure of the authors to a national audience.

JCPhP solicits and accepts manuscripts across a wide variety of subjects related to pharmacy practice and pharmaceutical research, and aims to provide an “open-format platform” of ideas. Article departments include original research, reviews, case reports/series, evidence-based practice, clinical practice capsules, law updates, and precepting pearls. If you would like to submit something to the Journal for consideration, but it does not seem to fit into any of these categories, we also have a special articles department.

We welcome submissions from all: faculty at schools and colleges of pharmacy, student pharmacists, and pharmaceutical researchers. I strongly encourage you to consider submitting your manuscripts to the Journal for publication. In addition, the Journal is always looking for individuals to help serve on our advisory board or as peer reviewers. More information about the Journal, as well as how to get more involved, can be found at www.jcphp.com. Please feel free to reach out to me or to Journal staff with any questions you may have. We look forward to your submissions to help further advance patient care. We hope you enjoy this new publication!

Sincerely,

Karl Hess, PharmD, APP, FCPhA
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Keck Graduate Institute School of Pharmacy
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Journal of Contemporary Pharmacy Practice  |  vol. 64, no. 1  |  www.jcphp.com
Evaluation of an Outpatient Pharmacy Clinical Services Program on Adherence and Fractures among Patients with Osteoporosis

Michele M. Spence, PhD; Abir F. Makarem, PharmD; Stacie L. Reyes, PharmD; Courtney Nguyen, BA

Purpose
Prior research has shown that low adherence to osteoporosis medications is associated with increased fracture risks. The objective of this study was to evaluate the impact of an outpatient pharmacy clinical service (OPCS) on medication adherence and fractures among patients with osteoporosis.

Methods
This study compared patients who received OPCS consultations upon picking up a new osteoporosis prescription at Kaiser Permanente Orange County pharmacies to usual care patients without an OPCS consultation. Three patients from the usual care group were matched to each patient in the OPCS program based on age, gender and whether or not they had a previous medication for osteoporosis within six months before the index date (new or prior users). Medication adherence and risk of fracture were compared using multivariate logistic regression. The analysis was conducted for the full cohort and by new and prior users.

Results
Among 1,172 OPCS and 3,302 usual care patients, we found no significant difference in adherence between OPCS and usual care patients in the full cohort or among prior users. Among new users, the OPCS group was significantly more likely to be medication adherent compared to the usual care group (OR = 1.23; 95% CI 1.05 – 1.44; p =0.012). We found no significant differences in risk of fracture.

Conclusion
Outpatient pharmacists are in a strategically excellent position to implement case management strategies to improve suboptimal adherence for patients with osteoporosis. Patients who initiate medications may be the best candidates for such interventions.

Introduction
Despite the favorable efficacy associated with osteoporosis medications, patient adherence remains suboptimal. Adherence rates to osteoporosis medications range from about 40 to 70 percent.1 Reasons for nonadherence are numerous and may include medication side effects, dosing requirements, and a perceived lack of benefit for an asymptomatic disease. Poor adherence is associated with increased fracture risks, and interventions designed to reduce fractures, including improved medication adherence, can ultimately improve quality of life and help curb osteoporosis-related costs.2,3 Because of their specialized knowledge of medications and access to patients, outpatient pharmacists are well positioned to coach patients in overcoming barriers to adherence. A systematic review of randomized controlled trials that examined the impact of pharmacist interventions on osteoporosis management found that pharmacists may improve bone mineral density testing and calcium intake.4 The authors note, however,
that none of the interventions examined treatment adherence. A more recent study of 13 Dutch community pharmacies found that pharmacists can decrease nonadherence with and discontinuation of osteoporosis medication through counseling sessions and monitoring of drug use. Additionally, a randomized controlled trial reported an increase in adherence for the pharmacist intervention group but no difference in persistence with osteoporosis medications. None of these studies examined the impact on fractures. In this study, we evaluate the impact of an outpatient pharmacy clinical service (OPCS) program on patient medication adherence and fractures among patients with osteoporosis.

Methods

Description of the Outpatient Pharmacy Clinical Services Program
The Outpatient Pharmacy Clinical Services (OPCS) program incorporates quality clinical services within the daily outpatient pharmacy workflow at Kaiser Permanente. The program focuses on improving medication adherence, safety and clinical outcomes among members with chronic diseases. Pharmacists provide face-to-face consultations that focus on medication adherence during patient visits to the outpatient pharmacy. A previous study has demonstrated the effectiveness of the OPCS program in improving medication adherence and clinical outcomes among patients with diabetes and dyslipidemia.

To impact adherence to osteoporosis drugs and reduce fractures, a pilot program has been started at Kaiser Permanente Orange County (KPOC), California. Outpatient pharmacists engage members picking up their first prescribed osteoporosis prescription in an expanded B-SMART (Barriers, Solutions, Motivation, Adherence Tools, Relationships, and Triage) consultation, which has been described in previous studies. In short, the B-SMART methodology is a multifaceted approach used by the OPCS pharmacists to help patients more effectively use their medications. Pharmacists use a checklist during the consultation to confirm: 1) benefits of treatment to prevent fractures and improve bone strength, 2) proper use of prescribed medications and importance of adherence, 3) the need to refill the prescription in a timely manner before running out, 4) importance of daily intake of calcium and vitamin D, including a proper diet, 5) benefit of regular weight-bearing and muscle-building exercise, 6) smoking cessation, and 7) home hazard proofing to minimize fracture risks. A crucial aspect of the consultation is that OPCS pharmacists address potential common barriers that contribute to drug nonadherence and discuss patient-specific solutions with each patient. Common identified barriers include forgetfulness, side effects, denial of condition, financial challenges, a lack of social support, complex medication regimens and poor health literacy. To support patients in better drug adherence and in being successful in the management of osteoporosis, pharmacists triage patients with concerns regarding their osteoporosis treatment to health education classes, smoking cessation classes, or to their primary care physician to have further discussions. Pharmacists document their consultations for data gathering and subsequent analysis.

Prior to providing OPCS osteoporosis consultations, pharmacists participate in 3.5 hours of online and face-to-face training. The training includes osteoporosis clinical management review and related clinical competency, training on the B-SMART consultation methodology that incorporates motivational interviewing, and workflow training to optimize the integration of OPCS osteoporosis consultations within existing outpatient workflow.

Identification of Study Cohort
The setting for this study was the KPOC service area, which provides care to approximately 530,000 members. We used a retrospective database analysis that compared patients who received OPCS consultations to similar patients from KPOC who did not receive an OPCS consultation (usual care). A list of medical record numbers for consulted patients identified the OPCS group. To be entered into the cohort, patients were required to have at least one prescription for an osteoporosis-related medication from January 1, 2012, through December 31, 2013. Initial medications included oral and nasal forms of
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alendronate, calcitonin, etidronate, ibandronate, raloxifene, and risedronate. We excluded patients with a diagnosis of cancer, Paget’s disease, or who were in hospice care. For the OPCS group, the index date was defined as the first consultation from January 1, 2012, through December 31, 2013, and for the usual care group, the index date was defined as the date of the first osteoporosis medication during the same time period.

We included patients who were 18 years of age or older and had continuous health plan enrollment and a drug benefit for one year before and after the index date. Patients in the OPCS group were then matched to three patients in the usual care group based on patient age, gender and whether or not they had a previous medication for osteoporosis within six months before the index date. Patients were followed for one year after the index date. For the follow-up period, we included the same types of medications as the index medications, plus any injectables or infusions such as denosumab, teriparatide, pamidronate or zoledronic acid.

Outcomes
Our primary outcome was adherence to osteoporosis medications one year after the index date and was defined as having a medication possession ratio (MPR) ≥ 0.80. The MPR was calculated as the sum of the days of medication supply divided by the number of days between the first fill and last refill plus the days' supply of the last refill. The average time from the index date to the first prescription fill after the index date was analyzed, and the percent of patients with a timely fill was compared. If the first prescription after the index date was filled within 30 days after the end of the days' supply of the index prescription, then it was considered a timely fill. The percent of patients who discontinued their osteoporosis medications was also compared. We used a 30-day gap to determine timely fill as well as discontinuation. If there was no refill after the index date or if a gap of 30 days or more occurred during the study period, then it was considered discontinued. Finally, we compared the proportion of patients in each group who had only one fill of an osteoporosis medication.

The secondary outcome was whether or not the patient had a fracture one year after the index date. Fractures were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) principal diagnosis codes from any inpatient or outpatient data source. We included pathological fracture (733.1x), stress fracture (733.93, 733.94, 733.95, 733.96, 733.97, 733.98), spinal fracture (805.x, 806.x, 807.x, 808.x, 809.x), and fracture of the upper limb (810.x-819.x) and lower limb (820.x-828.x).

Statistical Analysis
Comparisons between the OPCS program and usual care were made using Pearson chi-square tests for differences in percentages and t-tests for differences in means. Baseline characteristics such as age and gender were compared between the OPCS and usual care groups. To ensure that patients were similar at baseline, we compared the average Charlson Comorbidity Index (CCI), which is a measure of comorbidity and includes patient encounter-based indicators for a variety of chronic conditions, including coronary heart disease, heart failure, diabetes and hypertension, as well as potentially life-threatening conditions such as AIDS, kidney disease, and liver disease. Higher scores denote a greater number of severe comorbid conditions. A two-tailed P value of 0.05 was used to determine statistical significance. Using the primary outcome of adherence (percent of patients with an MPR ≥ 0.80), we estimated that we would need about 362 patients in each group (OPCS and usual care) to detect a 10 percent difference in adherence at 80 percent power and an alpha level of 0.05.

Multivariate analysis of the effect of OPCS consults on medication adherence was conducted using logistic regression. Covariates included age, gender, CCI, prior fracture, and prior use of osteoporosis medications. Logistic regression was also used to explore the risk of fracture, controlling for the same covariates, plus a measure of adherence to osteoporosis medications six months prior to the index date. We also conducted subgroup analyses among those patients who were new users (no prescriptions for an osteoporosis medication six months prior to the index date) and those who had previously used osteoporosis medications. Based on the logistic regression results, we reported patient characteristics associated with adherence and risk of fracture. All analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, North Carolina). The Institutional Review Board of KPSC approved this study.

Results
There were 1,172 patients in the OPCS group and 6,426 in the usual care group after inclusion and exclusion criteria were applied. We then matched one OPCS patient to three usual care patients based on age, gender and whether patients were either new or prior users, which resulted in 1,172 OPCS and 3,302 usual care patients in the final study cohort. There were 878 OPCS and 2,433 usual care new users and 294 OPCS and 869 usual care prior users. After matching, there were no significant differences between the two groups at baseline (Table 1). Most patients were female (80%), and their ages ranged from 37 to 98 years (mean = 72 years).

Descriptive analyses shown in Table 1 indicate that the OPCS group was more likely to have a timely first fill after the index date compared to the usual care group (74.2% vs. 70.5%, p = 0.039). There were no other significant differences for medication adherence in the full cohort. However, among patients who were new users of osteoporosis medications, the OPCS group was significantly more likely to be adherent one
year after the index date (37.7% vs 32.8%, p = 0.009), have a higher average MPR (0.75 vs. 0.72, p = 0.011), fewer days to first fill after index (108 vs. 117, p = 0.01), and a timely first fill (74.5% vs. 65.4, p < 0.001) compared to the usual care group. OPCS patients also had a longer mean days of therapy (196 vs. 177, p = 0.001) and were less likely to discontinue their osteoporosis medications (72.8% vs. 77.7%, p = 0.003). Among prior users, usual care was favored in some of the adherence measures. Compared to usual care, OPCS prior users were less likely to have a timely first fill (73.6% vs. 81.1%, p = 0.011), shorter mean days of therapy (240 vs. 274, p = 0.001), more likely to discontinue their medications (58.5% vs. 51.1%, p = 0.028) and more likely to have only one fill (12.2% vs. 7.6%, p = 0.015).

Multivariate analysis of the full cohort showed no significant difference in drug adherence between OPCS and usual care patients (Table 2). Among new users, the OPCS group was significantly more likely to be medication adherent compared to the usual care group (OR = 1.23; 95% CI 1.05 – 1.44; p =0.012), but this finding did not occur among prior users where the difference was not significant. Patient characteristics associated with adherence included male gender and lower CCI scores for both the full and new user cohort and prior fracture for the new user cohort, and, in the full cohort, prior users of osteoporosis medications were also significantly more likely to be adherent in the year after the index date compared to new users.

We found no significant differences between the OPCS and usual care groups in the percent of patients who had a fracture (Table 1) or in the risk of fracture (Table 2). In the full cohort, older age and having a prior fracture were significantly associated with an increased risk of fracture. Patients who were adherent to their osteoporosis medications were at reduced risk of fracture. The same patterns occurred in the new user cohort. Among prior users, only prior fracture was significantly associated with an increased risk of fracture.

**Discussion**

Results from this study show that the OPCS program was most effective among new users of osteoporosis medications. We found that 38% were adherent one year after the OPCS consultation, compared to 33% in the usual care group, and this effect held after controlling for covariates (OR 1.23; 95% CI 1.05-1.44). The OPCS program also improved the time to first fill and discontinuation rates. Among prior users, however, we found some favorable results for usual care, including a reduction in time to first fill and discontinuation, and an increase in mean days of therapy. Why would prior users in the usual care group have these improvements? A post-hoc analysis revealed that 9% of the OPCS group switched from oral alendronate to calcitonin nasal spray, compared to 1% of the usual care group (p< 0.001). Studies have shown reduced adherence with this medication, and one possibility is that we found a similar pattern in the OPCS patients. Future studies should be designed to identify which differences in drug type and dosing have the greatest impact on improved adherence.

Our results are similar to two previous studies. The MeMO program was composed of tailored counseling sessions by pharmacists and continuous monitoring of patients initiating osteoporosis medications. They found that 19% of patients in the MeMO program discontinued their medications or were nonadherent, compared to 32.8% in the usual care group. While it is difficult to directly compare these measures to ours, it appears that their rates of medication discontinuation and nonadherence were lower than what we found. Their program included continuous monitoring, which has not been incorporated into our pilot program. A randomized controlled trial among new users of osteoporosis medications found a higher rate of adherence for the pharmaceutical care group compared to a control group (98% vs 96%; p = 0.047). These high rates of adherence may be due to the method of assessing adherence (self-reporting), continuous monitoring, and the rigorous experimental setting. While our observational study depicts a more practice-based scenario that reflects real-world clinical care and patient behavior, continuous monitoring may be necessary to improve adherence in the long run.

We found no significant differences in fracture rates between the OPCS group and the usual care group. The sample size may have been too small to adequately detect fracture outcomes. Alternatively, patients were followed for one year, which may not be long enough to detect any significant difference in this important clinical outcome.

**Limitations**

Because patients were not randomized to the OPCS group versus the usual care group, it is possible that the results were attributable to systematic bias introduced by selection into the usual care group versus the OPCS group or that the two groups differed in other ways, such as socioeconomic status or educational levels, which may have affected patients’ ability to adhere to their medications. Although the two groups were similar at baseline, a limited number of baseline factors were included, and we did not employ additional methods such as propensity scoring to further control for potential confounding. Nonpharmacological factors that could act as confounders were not assessed. This could include physical activity, diet, BMI, smoking and family history.

**Conclusion**

In summary, outpatient pharmacists are in a strategically excellent position to implement case management strategies to
Table 1. Baseline characteristics, adherence and fractures of patients consulted by Outpatient Pharmacy Clinical Services (OPCS) compared to usual care patients. Mean ± standard deviation and column percentages reported.

<table>
<thead>
<tr>
<th></th>
<th>Full Cohort</th>
<th>New Users&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Prior Users&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPCS</td>
<td>Usual Care N = 1,172</td>
<td>OPCS N = 878</td>
</tr>
<tr>
<td></td>
<td>Usual Care N = 3,302</td>
<td></td>
<td>Usual Care N = 2,433</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>72±10.2</td>
<td>72±9.9</td>
<td>72±10.1</td>
</tr>
<tr>
<td></td>
<td>(79.7%)</td>
<td>(80.5%)</td>
<td>(79.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>934 (79.7%)</td>
<td>2,658 (80.5%)</td>
<td>696 (79.3%)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.76±1.2</td>
<td>0.81±1.3</td>
<td>0.75±1.2</td>
</tr>
<tr>
<td>Prior Fracture</td>
<td>149 (12.7%)</td>
<td>453 (13.7%)</td>
<td>121 (13.7%)</td>
</tr>
<tr>
<td>Prior Users&lt;sup&gt;b&lt;/sup&gt;</td>
<td>294 (25.1%)</td>
<td>869 (26.3%)</td>
<td>174 (59.2%)</td>
</tr>
<tr>
<td><strong>Adherence Measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherent</td>
<td>505 (43.1%)</td>
<td>1,353 (41.0%)</td>
<td>331 (37.7%)</td>
</tr>
<tr>
<td>MPR</td>
<td>0.77±0.2</td>
<td>0.76±0.2</td>
<td>0.75±0.3</td>
</tr>
<tr>
<td>Days to first fill after index</td>
<td>105±64.9</td>
<td>110±65.2</td>
<td>108±56.8</td>
</tr>
<tr>
<td>Timely first fill</td>
<td>633 (74.2%)</td>
<td>1,735 (70.5%)</td>
<td>443 (74.5%)</td>
</tr>
<tr>
<td>Mean days of therapy</td>
<td>207.3±146.6</td>
<td>202.9±146.7</td>
<td>196.0±142.8</td>
</tr>
<tr>
<td>Discontinued</td>
<td>811 (69.2%)</td>
<td>2,334 (70.7%)</td>
<td>639 (72.8%)</td>
</tr>
<tr>
<td>One fill only</td>
<td>318 (27.1%)</td>
<td>841 (25.5%)</td>
<td>282 (32.1%)</td>
</tr>
<tr>
<td><strong>Fractures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Fracture</td>
<td>95 (8.1%)</td>
<td>296 (9.0%)</td>
<td>76 (8.7%)</td>
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</table>

<sup>a</sup>Patients without any osteoporosis medications 6 months before index date. <sup>b</sup>Patients with osteoporosis medications 6 months before index date. MPR = Medication Possession Ratio.

Table 2. Multivariate results for adherence<sup>a</sup> to osteoporosis medications and risk of fracture one year after index date.

<table>
<thead>
<tr>
<th></th>
<th>Full Cohort</th>
<th>New Users&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Prior Users&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>Odds Ratio</td>
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<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>p-value</td>
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<tr>
<td><strong>Adherence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPCS</td>
<td>1.11</td>
<td>0.96-1.27</td>
<td>1.23</td>
</tr>
<tr>
<td>Age</td>
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<td>0.99-1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Male</td>
<td>1.37</td>
<td>1.17-1.59</td>
<td>1.48</td>
</tr>
<tr>
<td>Prior Fracture</td>
<td>0.90</td>
<td>0.75-1.09</td>
<td>0.98</td>
</tr>
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<td>Charlson Comorbidity Index</td>
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<td>0.88-0.98</td>
<td>0.93</td>
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<tr>
<td>Prior User</td>
<td>3.26</td>
<td>2.83-3.75</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Risk of Fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPCS</td>
<td>0.93</td>
<td>0.73-1.19</td>
<td>0.96</td>
</tr>
<tr>
<td>Age</td>
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<td>1.01-1.03</td>
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<td>0.77</td>
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<td>Prior User</td>
<td>0.93</td>
<td>0.71-1.21</td>
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<sup>a</sup>Adherence defined as having medication possession ratio of 80% or greater. <sup>b</sup>Patients without any osteoporosis medications 6 months before index date. <sup>c</sup>Patients with osteoporosis medications 6 months before index date. OPCS = Outpatient Pharmacy Clinical Services; CI = Confidence Interval.

<sup>a</sup>Patients without any osteoporosis medications 6 months before index date. <sup>b</sup>Patients with osteoporosis medications 6 months before index date. <sup>c</sup>Patients with osteoporosis medications 6 months before index date. OPCS = Outpatient Pharmacy Clinical Services; CI = Confidence Interval.
improve suboptimal medication adherence among patients with osteoporosis. By engaging patients with a new osteoporosis medication during a face-to-face consult, the OPCS pharmacist was able to influence and improve medication adherence.

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5. Stuurman-Bieze AGG, Hiddink EG, van Boven JFM, Vegter S. Proactive pharmaceutical care interventions decrease patients’ nonadherence to osteoporosis medication. Osteoporos Int. 2014; 25:1807-1812


Specialty medications are complicated, treat complicated diseases, and are costly. Yet, even if their cost was to be decreased by 50%, many of the specialty medications would still be too costly either with high copays, or be unaffordable under any circumstance. Hence the use and oversight of Specialty medications is more complex than just cost: effectiveness, risk and cost must be evaluated concurrently. Utilization is actually the great multiplier. No matter the individual cost of a medication, uncontrolled expansion of medication use leads to more drugs, and therefore, higher drug spend. Utilization management of Specialty medications is, thus, a multifactorial process that is as important as cost management.

Human Insulin was the first of the so-called “Specialty Medication.” Specialty treatments followed for orphan and previously untreated diseases. Treatments for chronic diseases followed where Specialty medications replaced older small molecules. The major complication was that the cost of these new treatments rivals, and often exceeds, acute care hospital stays. Unfortunately, evidence has not always matched the comparative benefits of Specialty medications over their small molecule counterparts. As a result, the explosion of new Specialty medications has also stimulated the need for strong evidence that these medications are significant improvements over prior therapies. If so, how can they be affordable?

Utilization management of Specialty medications shares many of the same elements that have been used for decades to monitor and manage all treatments; namely, prior authorization, drug utilization review, step therapy, and quantity limits. This paper will examine the approach to utilization management of Specialty medications with the goals of providing a template for providers to participate in this management as well as to understand the metrics applied when these medications are submitted for payment.

Definition

Utilization management is a tool for evaluating therapy for effectiveness while also monitoring for the risk introduced by these treatments. As treatments have become more expensive, utilization management has also become a euphemism for cost control. Yet, utilization management is not without definition. Utilization was defined in the Omnibus Budget Reconciliation Act of 1990, Section 4401, known as Obra 90. This law contained the requirement for prospective drug utilization review that included:

- Therapeutic Duplication
- Drug-Disease Contraindications
- Drug-Drug Interactions
- Incorrect Drug Dosage
- Incorrect Duration of Treatment
- Drug-Allergy Interactions
- Clinical Abuse/Misuse of Medication

In order to implement the Obra 90 requirements tools were developed to “manage” utilization. The motivation for these tools and methods is frequently cost control, but the rationale can usually be anchored to a need for risk management. As a result, Drug Utilization Review (DUR) must cover the prospective, concurrent, and retrospective use of medications throughout the patient’s experience. As such, the definition of DUR in Obra 90 has been expanded to include common benefit tools supporting formularies, especially restricted formularies of various designs. Common tools employed by insurers are:

- Maximum Number of Medications Allowed
- Prior Authorization based on usage criteria
- Step Therapy (ST)
- Quantity Limits (QL)
- NDC blocks
- Medication Refill Limits
- Max Dollar Limits

Specialty medications have expanded the need for deployment
of these tools and caused payers to reach back to the original tests applied for all therapy: namely, FDA approvals for medications and uses, effectiveness and comparative effectiveness, and tests for risks of these treatments. [Figure 4]

**Metrics Used for Management**

The approval of Specialty medications has driven the need for merging elements of Pharmacy and Medical benefits. Merging benefits brings its own complications requiring data and metrics to manage these benefits. The broad metrics used by insurers that are applicable for management of Specialty medications in merged medical/pharmacy benefits are [Figures 2, 3]:

- Total Amount Paid overall and by channel
- Per-member-per-month (PMPM) and per-year (PMPY)
- Per utilizerr-per-month (PUPM) and per-year (PUPY)
- Location of Service – Paid/claim and PUPM
- Top Diagnoses – Paid/claim and PUPM
- Top providers, specialties, medications, and related procedures – Total paid, paid/claim, paid/unit, PUPM, #Rx PUPM
- Comparative Unit Price and Discount by Channel / Sub-channel – ASP, AWP / WAC, AMP, NADAC and AAC

The list of metrics is dynamic and requires trending as well as benchmark comparisons. Of particular concern is how these metrics are calculated and applied. Standardization by data aggregators, surveyors, and health plans is crucial so that appropriate comparators are applied. These metrics are, and will also be, applied to benefit designs utilizing best-in-class (BIC) and centers of excellence (COE) to improve quality and achieve performance improvement. These designs have been used in medical benefits for some time, so it will be no surprise that the cost as well as complexity of diseases and conditions utilizing Specialty medications as the primary vehicle for management will drive BIC and COE care delivery models. [Figure 1]

**Effectiveness and Benefit Compliance**

The first consideration for providers and insurers is the effectiveness of Specialty medications and their compliance with benefit definitions. The primary tests used by insurers are:

1. Diagnosis ICD10 Billed vs. Expected ICD10 for the prescribed medication
2. Dosage and duration billed consistent with usage for ICD10 billed
3. Benefit / Formulary compliance

As a result, prescribers and pharmacists must ensure that any Specialty prescription complies with these tests. Utilization management uses these tests to determine if the medication is being used for FDA approved package labeled vs. off-label uses and if benefits cover the diagnosis in the claim. Dosage tests for Specialty require more than the traditional tests for prescribed dosages that are greater/lower than the maximum/minimum labeled dosages. The tests evaluate dosage for the specific condition prescribed as compared to the possible dosages for the multiple conditions that a Specialty medication may treat. In addition, the tests evaluate the dosage when the medications are used in combination as with cancer chemotherapy. The benefit compliance tests must also determine if there is a violation of quantity limits, duration of therapy, and step therapy requirements when applicable. The result of these tests is an approval of a prior authorization; hence it is crucial that prescribers and pharmacists ensure that merged information from medical and pharmacy benefits are accounted for in the prescribing decision.

Specialty medications are often used in concert with other medications and non-medication therapy. As a result, individual medications are not evaluated in isolation, but as part of a regimen. These regimens, especially pertinent to cancer chemotherapy, are evaluated by the three effectiveness tests above as applied to the entire regimen. Evidence-based guidelines assume a significant role in the prescribing, utilization oversight, monitoring, and benefit approval of therapeutic regimens. The use of Specialty medications as solo treatments and as part of regimens places further emphasis on the evidence-based tools applied to benefit approvals. Therefore, prescribers and pharmacists must pay attention to the evidence supporting the use of Specialty medications for various conditions, and must also be familiar with NCI, NCCN, and national guidelines for usage of these medications. Clearly, the cost of these medications requires that they be used when there is significant evidence of benefit and acceptable risk. [Table 1]

**Risk**

The consideration of risk is not separate, but coordinated with the evaluation of effectiveness. Specialty medications treat high risk conditions like various cancers, hepatitis, and multiple sclerosis. They also contribute higher additional risk than small molecule therapy due to higher probabilities of allergies, adverse drug reactions, and drug-induced conditions. As a result insurers return to Obra 90 tests for claims with inadequate/super dosages, extended durations leading to unnecessary exposure to medication effects, duplications leading to increased chances of additive side effects, polypharmacy risks for drug-induced problems, and adverse drug interactions. It is incumbent on all providers to include an aggressive plan for surveillance and management of these risk factors in order to minimize overall risk.
Figure 1. Sample Management Metrics

Table 1. Sample Guideline Sources


Table 2: Benchmark References

1. Avalere Health. Available at: www.avalerehealth.com

2. Deutsche Bank, 2015 Survey. Available at: www.db.com

3. EMD Serono Available at: www.emdserono.com

4. ICER (Institute for Clinical & Economic Review) Available at: www.icer-review.org

5. IMS Health. Available at: www.imshealth.com


HyGen Pharmaceuticals, Inc.


1-877-630-9198
www.hygenpharma.com
Due to the enhanced chances of risk from Specialty and other medications the FDA has required Risk Mitigation and Evaluation Strategies (REMS) from manufacturers for specific medications. By definition “The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.” When a medication has a required REM the prescriber and pharmacist must fulfill specific requirements for surveillance as well as educating the patient to ensure that the risk of drug-induced problems is minimized. The provider, i.e., physician and pharmacist, certification requirements of each REM add a specific utilization approach to each applicable medication.2

Effectiveness / Risk / Affordability

Utilization management of Specialty medications encompasses the broad set of surveillance and management metrics identified above. It could also be argued that Specialty medications must be viewed under the lens of merged medical and pharmacy benefits that require concurrent evaluation of effectiveness, risk and affordability. This type of evaluation requires more information and communication between all providers. Traditional claims information must be supplemented with patient-specific information derived from electronic medical records (EMRs), the results of biometric screening, and patient supplied information from electronic health records (EHRs) and health risk assessment questionnaires (HRAs). A standard language is required to digitally integrate all of this information.

The Unified Medical Language System® (UMLS®) was designed for this purpose as an international standard. As a component of this system the Systematized Nomenclature of Medicine (SNOMED) vocabulary provides a systematic library of medical terms, in computer processing language, “for human and veterinary medicine, to provide codes, terms, synonyms and definitions which cover anatomy, diseases, findings, procedures, microorganisms, substances, etc.” The UMLS® also contains RxNORM that contains standard names for drugs that do not change with NDC so that EMRs, drug interaction databases and pharmacy computer system software can talk to each other.3,4

All pharmacy computer software and medical EMRs will have to be programmed to communicate in these languages. The result is an international movement of managed care principles into individual patient and population management. Medication Therapy Management (MTM) and Comprehensive Medication Review (CMR) must be cast into these languages and will be enhanced by the integrated data available from the EMRs and HRAs. In addition, laboratory data is undergoing a similar codification and language standardization through the Logical Observation Identifiers, Names and Codes or LOINC®. This standard coding system will help to facilitate the incorporation of laboratory findings into the overall evaluation of care both individually and in populations. This includes the genomic testing required for selection of those Specialty medications used to treat applicable diseases.

However, while common languages are being deployed there are utilization tests that incorporate elements of effectiveness, risk, and the resultant affordability of Specialty medications. Surveillance for drug-induced disease, and adverse drug reactions, is paramount for new clinical findings in diseases treated with Specialty medications as well as the first consideration in the differential for new symptoms in elderly patients. In addition, the universe of opportunities for drug interactions now includes medications used in both medical and pharmacy environments. This merging of experience also reflects usage, or lack thereof, where patients take drug holidays and fail to adhere to prescribed regimens. The complexity of regimens including Specialty medications, enhanced side effects, and affordability all contribute to usage concerns.

The metrics that insurers may use to evaluate the coordinated utilization of Specialty medications are commonly calculated from codes in claims data, and while there is no generally accepted metric profile at present, many metrics are reported. Providers may receive some or all of this information from Health Plans or Pharmacy Benefit Managers (PBMs). For example:

- **Effectiveness:**
  - Compliance with common quality metrics such as HEDIS, PQA
  - % denials
  - % required genomic testing
- **Cost** [Figure 2]:
  - Cost per-utilizer-per-month (PUPM)
- **Utilization:**
  - Number of prescriptions per-utilizer-per-month (Rx PUPM)
  - Compliance %, Drug Holiday %, Terminated therapy %
- **Risk** [Figure 5]:
  - Efficiency of clinical flags (trended percent of flagged clinical problem to total claims)
  - Rate of important drug interactions and drug-induced conditions to total claims

These metrics are calculated after the fact and benchmarked to medical practices with similar patient populations (age/gender), severity of illness, disease patterns, and geographic proximity.

Individual physicians and pharmacists (i.e., providers) can calculate their own statistics from quarterly or annual reviews.
of their own data. This is not an academic exercise as the comparison of individual practice metrics with those published by insurers, PBMs, or CMS can lead to quality improvements, revenue enhancement, as well as defensive maneuvers to support individual practice excellence. Note that it is not always clear what actions are necessary to improve these metrics. Health Plans and PBMs may report results, but specific actions may not be evident. As a result, providers should communicate with Health Plans to determine action plans for improvements and maintain their own records to substantiate progress toward objectives.

**Fraud, Waste, Abuse (FWA)**

Due to the cost of Specialty medications it is no surprise that insurers, CMS and states are focused on potential fraud, waste and abuse (FWA). FWA analysis is both surveillance for actual fraud and deployment of measures to prevent waste and abuse. Any deviations from averages are a potential target as are providers who display deviations from expected norms. For example providers are reviewed for practices that deviate to a large extent from matched norms:

- **Cost**
  - Cost per claim exceeds expected norms
  - PUPM cost exceeds comparable provider practices

- **Fraud or Abuse**
  - Providers with a high percentage of off-label use
Claims exceed QL and/or expected frequency
Claims with zero quantity
Claims with invalid NPI and/or NDC
• Duplicate charges – pharmacy/medical
• # packages paid exceeds comparable locations of service

Arguably, the FWA analyses are a subset of utilization management focused on cost and utilization outliers. Since proving fraud is a lengthy legal process, prevention is the less costly, less resource intensive, and most efficient method for self-correction of outlier performance. Yet prevention is more than identification of high probability providers. It requires behavior modification, and correction of standard or regulatory processes and requirements used by payers that lead to wasteful and abusive practices. Providers should strongly consider re-evaluation of all practices that might fall under any element of FWA and address corrections within their practices. Claims analysis, standardization of data, and the explosion of fraudulent claims submissions are placing a greater emphasis on all providers to be more compliant.

Future Opportunities
The future of utilization management shares a common path for both small molecule and Specialty medications. Considering utilization management as more than decreasing the number of duplicate medications or switching to less costly options, the merging of medical and pharmacy benefits is leading to additional opportunities for competition to control utilization.

Channel competition, whether between medical and pharmacy or between sub-channels, is a market mechanism to control utilization and cost. Pharmacy sub-channel competition between specialty pharmacies, network pharmacies, and PBMs is in its infancy. Pricing competition, access to Specialty pharmaceuticals, provider service, compliance/adherence, and distribution are the current emphases. However, medical sub-channel competition between locations of service (e.g., physician offices, infusion centers, emergency medicine, hospital outpatient, acute care hospitals) is mature and hotly contested. Medical competition targets best-in-class (BIC) and centers of excellence (COE) to provide measurably better care and outcomes at competitive prices. Ultimately, and in short order, it is expected that all channels will be competing over clinical and process outcomes.

The demand for information is creating digital data sharing including performance and cost based pricing “supermarkets.” AHRQ historically and the Affordable Care Act both emphasize information sharing between providers – physicians and pharmacists as well as teams of providers in Accountable Care Organizations (ACOs) and medical homes (PCMH) – as
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This innovative and interactive program is designed to equip pharmacists with the skills necessary to become primary sources for vaccine advocacy, education, and administration.

▶ october 14
los angeles, ca

▶ november 4
san francisco, ca

register online now: bit.ly/immunization-cpha
### Figure 4. Common Claims Payment Problems

<table>
<thead>
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<th>PMPM</th>
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### Figure 5. Sample Risk Results From Clinical Assessment

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well as comparison of clinical quality performance across all channels. The desired result is better care, which means measurable comparative utilization with the beneficiary being lower comparative cost.

The cost of Specialty medications creates a need for cost comparisons, e.g., national pricing (ASP, NADAC, 340b), state Medicaid pricing (AAC, Specialty MAC prices), and PBM/Health Plan prices. The expansion of the biosimilar market, once naming and coding conventions are decided, will add comparative pricing to these “supermarkets.” This additional “transparency” in pricing is expected to apply market controls to Specialty medications similar to managed care market-based models.

Conclusion

If utilization is the great multiplier of cost and resource consumption, then utilization management is the answer to what to do after volume discounts and rebate negotiations to decrease net cost. Specialty medications are the poster child for cost control and utilization management. As a result, the application of utilization practices and the measurement of results will not be ignored.

All providers need to incorporate the integrated approach to utilization management into their practices. They need to keep tables of utilization metrics to document the outcomes of their practices. There is no doubt that insurers, compliance agencies and regulatory bodies will measure, benchmark, and publish results. The transparency of data sharing is, and increasingly will be, standard practice for management of Specialty Medications.

References


About the Author

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The End of Life Option Act: Important Considerations for Pharmacists as California Implements Physician Aid in Dying

Laura A. Petrillo, MD

On June 9th, 2016, California joined Oregon, Washington, Vermont and Montana as the fifth state to permit physician aid in dying.\(^1\) The California End of Life Option Act is modeled after the Oregon Death with Dignity Act, which was voted into law in 1994 and went into effect in 1997. Both laws make it legal for physicians to assist people in particular circumstances to end their lives (Figure 1). These circumstances include 1) the patient is an adult, California resident with a terminal illness, with a prognosis of six months or less 2) the patient has the ability to self-administer the aid-in-dying drug and 3) the request originates from the patient, not from the patient’s surrogate or anyone other than the patient. The law has safeguards intended to ensure that patients are acting autonomously, including a 15-day waiting period between two requests, the requirement that patients meet privately with their physicians to confirm they are acting on their own, and the requirement that patients sign a form within 48 hours of taking the aid-in-dying drug to indicate that it is their choice. The law also requires that patients receive a second opinion from another physician to confirm their eligibility. In addition, the law makes it a felony to knowingly coerce a patient to request physician aid in dying, to falsify a request or to administer the aid-in-dying drugs to a patient without their knowledge or consent.\(^1\)

How Other States Have Experienced Physician Aid in Dying

Oregon’s experience with nearly twenty years of the Death with Dignity Act provides one example of physician aid in dying in practice in the United States. In Oregon, individuals who have used physician aid in dying were most often white (96.6%), older adults (median age 71) with a cancer diagnosis (77%).\(^2\) Patients most commonly cited concerns about “losing autonomy” (91.6%) and “being less able to participate in activities that make life enjoyable” (89.7%) as motivation for their interest in physician aid in dying, according to data collected via physician report.\(^2\)

One positive outcome of the Death with Dignity Act in Oregon is that 91% of people who received a physician aid in dying prescription between 1998 and 2015 were enrolled in hospice at the time of death,\(^3\) which is double the national frequency of hospice enrollment.\(^4\) This achievement is a testament to the efforts of the Oregon healthcare community to improve end-of-life care generally in response to the legalization of physician aid in dying.\(^5\) One area of concern is the low frequency of psychiatric evaluations (5.3% over 1998-2015) for Oregon residents who received a lethal prescription through the Death with Dignity Act, despite the finding that depression is relatively common among requesters (26% of patients who made a request for physician aid in dying met criteria for clinical depression in one study).\(^6\)

Data from the Seattle Cancer Care Alliance indicate that about five-fold more patients inquire about physician aid in dying than use it.\(^7\) There are a variety of reasons for this difference: patients are unable to make it through the process due to illness progression, they do not qualify, they change their mind, or they find relief from their suffering from alternatives like pain control or hospice.\(^7\) Comprehensive attention to patients’ end of life needs by healthcare providers go a long way, not only to support patients and families\(^8\) but also, in some cases, to change patients’ minds about pursuing physician aid in dying.\(^8\)

What to Expect in California

Given the similarities between California’s End of Life Option Act and the Oregon and Washington laws, California’s experience with implementation of physician aid in dying is likely to resemble the other states’ in some ways. However, there are important differences between the states, including California’s size, its ethnic, cultural and socioeconomic diversity, and the variability in healthcare access across the state (Table 1). These differences may have an effect on how acceptable physician aid in dying is to patients, or how accessible it is. An opinion poll done in August 2015 indicated that 76% of Californians support physician aid in dying, but support was higher among white, Asian-American and Latino adults (all ≥75%) than among African-Americans (52.3%).\(^1\)
It is reasonable to expect that as in Oregon and Washington, many more patients will inquire about physician aid in dying than will use it in California. The long, contentious debate about the law and the recent rise in public support for the issue may mean that even more patients will ask their physicians about physician aid in dying in California. It is essential that healthcare providers fully explore the reasons behind a patient’s request and connect patients to resources like hospice, because many patients use the subject of physician aid in dying to bring up their fears about the future, rather than because they have a true interest in hastening death. In addition, for those who persist in their interest in physician aid in dying, hospice will help them in their remaining time before using the aid-in-dying drugs. An unfortunate, early case in San Diego underscored how important it is for healthcare providers to give dying patients support and anticipatory counseling in addition to a prescription; the patient’s family reported that they were in a “race against her symptoms” to obtain the aid-in-dying drugs and that her death was “fraught and frightening.” They were surprised that the aid-in-dying drugs themselves did not take away the anxiety and discomfort of the dying process, a reflection of incomplete understanding about the limitations of physician aid in dying.

One important aspect of California’s End of Life Option Act is that participation in the law is voluntary for healthcare providers, and the definition of “provider” includes clinics, health dispensaries and health facilities, in addition to individuals. Therefore every facility where patients receive healthcare, including pharmacies, may choose whether or not to participate in the law. And within facilities that have opted to participate, individual providers may choose to opt out. Religious and federal healthcare systems will not permit providers to participate in the law, which may lead to difficulty for patients in finding a physician to prescribe the aid-in-dying drugs. Already, since the End of Life Option Act has gone into effect, reporters have raised concern of a shortage of willing physicians in rural counties like Humboldt.

Several institutions have added requirements in addition to the law’s safeguards in order to further protect patients from harm, such as mandatory palliative care or mental health evaluations, or credentialing for physicians who participate. These requirements are intended to reduce the risk of patients receiving a prescription as a result of coercion or insufficient evaluation for reversible causes of suffering, but may make it more difficult for patients to obtain a prescription.

What Every Pharmacist Needs to Know

As described above, participation in the End of Life Option Act is voluntary. Any pharmacist may decline to participate for reasons of conscience, morality or ethics. The attending physician (the physician who ultimately writes the prescription) evaluate the patient’s capacity and ability to self-administer the aid-in-dying drug. This is to prevent harm to patients whose ability to make decisions is compromised by cognitive impairment or mental illness, and to prevent patients who cannot self-administer from receiving aid in dying against their will. The attending physician is required to deliver the prescription by hand or mail it to the pharmacy, and the patient must pick the aid-in-dying drugs up herself or designate an agent to pick them up.
up, or the attending physician can pick up the aid-in-dying drugs for the patient. If the patient designates an agent, the attending physician must inform the pharmacist of the agent’s name. The pharmacy may also mail the aid-in-dying drug with a signature required upon delivery.¹ Unlike Oregon, California does not require that pharmacists submit a form to document that an aid-in-dying drug has been dispensed.

If a pharmacist has concern about any aspect of the process, he or she should call the attending physician. If the pharmacist and the physician together have concern about coercion or that someone other than the patient intends to administer or use the aid-in-dying drug, they should not release the aid-in-dying drug and should report the suspected party to the police. If a pharmacist or anyone else has concern about an inappropriate prescription, such as to an incompetent or ineligible patient, or by a physician who does not have an “attending physician” relationship to the patient (treating the patient’s terminal illness), the pharmacist should report the physician to the California Medical Board.

As with any controlled substance, there is risk of harm to others in the patient’s household who may have access to the lethal drug. Bereaved family members in particular are at increased risk of suicide in the period after the patient’s death. Pharmacists can reduce the risk of harm by counseling patients’ families and caregivers about safe disposal of unused aid-in-dying drugs after the patient’s death. Pre-paid mailers would reduce the burden on families, but there are no state programs to cover the cost of safe disposal at this time.

The Law in Action: Pharmacy Updates

The choice of aid-in-dying drug is at the discretion of the prescribing physician (the law does not specify this level of detail). In Oregon, the most commonly used drug for the Death with Dignity Act has been a large dose of secobarbital.² In anticipation of legalization of physician aid in dying in California, the pharmaceutical company that makes secobarbital, Valeant, increased its price, and as a result, the out of pocket cost is now about $3,000.¹⁵

Because of the rising cost of secobarbital, proponents of physician aid in dying have been attempting to find new drug protocols. A cheaper combination of morphine, chloral hydrate and phenobarbital has been recently introduced in Oregon and used by 16 patients in 2015.³ Patients have reported a burning sensation with ingestion.¹⁶ The advocacy groups Compassion & Choices and Death with Dignity have suggested alternate protocols, such as large doses of opioids and tricyclic antidepressants.¹⁶,¹⁷ Though these are untested, and have limited to no data to support their use for this indication.

Whether insurance will cover physician aid in dying drugs is variable. Medicare will not cover physician aid in dying, nor will the Veterans Health Administration. Shortly after the End of Life Option Act passed, $2.3 million in funding for services related to the End of Life Option Act was included in the Medi-Cal budget to cover the cost of the aid-in-dying drugs.

Conclusion

The legalization of aid in dying through the End of Life Option Act represents a huge shift in the scope of end of life care for California. The law gives certain qualified patients more control over their death, and provides immunity for the healthcare providers who assist them. Healthcare providers are not obligated to participate in the law. Because of the potential for risk to patients and their families, the End of Life Option Act requires a tremendous amount of effort on the part of the healthcare system to ensure safe implementation. Healthcare providers who choose to participate, including pharmacists, should learn not only the law and its safeguards, but also the institutional policy and culture where they practice. Communication and collaboration among healthcare professionals is essential to keep patients safe.

Figure 1. End of Life Option Act Law Overview.¹

End of Life Option Act Overview

- Adults (≥18) with a terminal illness may request a drug to end their lives from their physician
- Patients must: have the ability to make decisions, have the ability to take the drug and not have impaired judgment due to a mental disorder
- Prognosis and decision making capacity must be confirmed by two physicians
- Patients must make two oral requests, 15 days apart, and one written request
- Physicians must counsel patients about alternatives, including comfort care, hospice care, palliative care, and pain control

About the Author

Laura Petrillo, MD, is a Palliative Care Physician at the San Francisco Veterans Affairs Medical Center and in the Division of Geriatrics at the University of California, San Francisco. She provided expert testimony in the California State Assembly hearing on the End of Life Option Act and has been a leading physician voice on safe implementation of the law. Dr. Petrillo has no conflicts of interest to report.
Table 1. Comparison of California with Oregon and Washington, the two states that have had the longest experience with physician aid in dying, including: population differences, demographic differences, palliative care availability, proportion of deaths at home, and physician aid in dying death data.

<table>
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<th>California</th>
<th>Oregon</th>
<th>Washington</th>
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</thead>
<tbody>
<tr>
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<td>7.06</td>
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<td>Race/ethnicity, %</td>
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<tr>
<td>Other</td>
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<tr>
<td>Hospitals with palliative care, %</td>
<td></td>
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<td></td>
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<tr>
<td>&gt;50 Beds</td>
<td>74%(168/227)</td>
<td>88.9%(24/27)</td>
<td>92.7%(38/41)</td>
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<tr>
<td>&lt;50 Beds</td>
<td>44.1%(15/34)</td>
<td>44.8%(13/29)</td>
<td>35.7%(10/28)</td>
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<tr>
<td>Sole community providers</td>
<td>33.3%(2/6)</td>
<td>100%(3/3)</td>
<td>80%(4/5)</td>
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<tr>
<td>Annual deaths</td>
<td></td>
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<td>% death at home</td>
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<td>Not available</td>
<td>857</td>
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<td>Physician aid in dying deaths, % of all deaths</td>
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<td>0.22%</td>
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</table>

References


The End of Life Option Act – The Pharmacist's Role

Tony J. Park, PharmD, JD

The Act

On June 9, 2016, terminally ill individuals in California acquired the legal means to end his or her own life provided certain conditions are met. Specifically, the End of Life Option Act (the “Act”) added section 443, et seq. to the California Health & Safety Code (“HSC”). The Act allows California residents diagnosed with a terminal illness and a survival prognosis of six months or less, to receive an “aid-in-dying drug” to end his or her own life in a nonpublic place.

Under the Act, the pharmacist’s role is limited, since the process for receiving a drug order for an aid-in-dying drug differs considerably from ordinary practice. However, while the Act is silent on the pharmacist’s legal responsibility to provide patient consultation, it clearly contemplates that an aid-in-dying drug be dispensed by a pharmacist in a community or outpatient setting. Given the irreversible finality of dispensing such drugs, the pharmacist should be assured that voluntary participation in the Act is in full compliance with its provisions, and the pharmacist will not be subject to retaliation, termination, or litigation. For these reasons, the pharmacist must understand the Act’s rigorous vetting requirements imposed on the attending physician to be able to ascertain whether any particular terminally ill individual is, or may be, qualified to receive an aid-in-dying drug, and to also appreciate the rigors imposed on the individual patient seeking to become qualified to legally receive a drug to end his or her own life.

What is an Aid-In-Dying Drug?

HSC § 443.1(b) defines an aid-in-dying drug as a “drug determined and prescribed by a physician for a qualified individual, which the qualified individual may choose to self-administer to bring about his or her death due to a terminal disease.” This definition, at first blush, may appear benign and somewhat unremarkable. However, it is important to view it through the prism of another definition offered by the Act: the meaning of “self-administer.”

Under HSC § 443.1(p), “Self-administer” means a qualified individual’s affirmative, conscious, and physical act of administering and ingesting the aid-in-dying drug to bring about his or her own death. The choice of aid-in-dying drug is decided by the attending physician based upon its determined effectiveness (or lack of a better description) and likelihood of achieving the desired outcome of death. However, the choice is equally based upon dosage form considerations, which may ensure that the qualified individual will be able to “affirmatively, consciously, and physically” take the drug orally and “ingest it.” The “affirmative, consciously, and physically” requirements immediately rule out anyone other than the qualified individual from physically handling the aid-in-dying drug or administering it. Further, the “ingest” requirement dictates the dosage form, ruling out any drugs administered intravenously, subcutaneously, intrathecally, transdermally, rectally, or any other dosage form other than that taken through oral ingestion. Profound obstructions to employ the rights afforded under the Act are created by the very definition of what the Act considers an “aid-in-dying drug.”

Individuals who endure a terminal illness that renders him or her unable to use his or her arms, hands, and fingers (or feet and toes, as the case may be) will likely be unable to “self-administer” an aid-in-dying drug. A strict interpretation of the language in HSC § 443.1(p) disqualifies individuals with such physical limitations from receiving an aid-in-dying drug. Arguably, patients who are unable to swallow would also be barred from qualifying under the Act. Still further, patients with gastrointestinal disorders that prevent drug absorption to the extent required for the chosen drug to have its intended life-terminating effect are also disqualified.

In the event that a pharmacist knows that an otherwise qualified individual is unable to physically self-administer the aid-in-dying drug consistent with the Act, the pharmacist should not furnish the aid-in-dying drug, because doing so in this context would fail to comply with technical requirements of the Act and could be construed as assisted suicide, which is unlawful in California. Accordingly, where the pharmacist has knowledge
of any physical limitation that prevents the patient from self-administering the aid-in-dying-drug, the pharmacist should confer with the attending physician and qualified individual.

### How to Become a “Qualified Individual”

The Act allows an individual with a terminal disease to request and obtain a prescription for a drug that the individual can self-administer to end his life only if pursuant to an informed patient decision after the attending physician fully informs the patient of all the following:

1. The individual’s medical diagnosis and prognosis.
2. The potential risks associated with taking the drug to be prescribed.
3. The possibility that the individual may choose not to obtain the drug or may obtain the drug but may decide not to ingest it.
4. The feasible alternatives or additional treatment opportunities, including, but not limited to, comfort care, hospice care, palliative care, and pain control.

Further, the qualified individual must be afforded ample opportunity to change his or her decision at any point before receiving, and even after receiving, an aid-in-dying drug. Specifically, the Act requires the qualified individual to submit at least two verbal requests to the attending physician at least 15 days apart and a written request for the aid-in-dying drug to the attending physician personally, and the patient may not delegate this responsibility to any other person.

Moreover, this written request must be made on a form described in detail within HSC § 443.11, and must be signed and dated by the qualified individual in the physical presence of two witnesses. Each of these two witnesses must attest in writing that, to the best of his or her knowledge and belief, the qualified individual is personally known to him or her (or the qualified individual has at least provided proof of identity to him or her), that the qualified individual has voluntarily signed the request for the aid-in-dying drug in his or her presence, that the qualified individual is of sound mind and not under duress, fraud, or undue influence, and that the witnesses are not the attending physician, consulting physician, or a mental health specialist. And lastly, no more than one of the two witnesses may be related to the qualified individual, nor entitled to a portion of that qualified individual’s estate upon his or her death, nor may the witness be an owner, operator, or employee at the healthcare facility where the qualified individuals is a resident or receiving medical treatment.

The Act also requires the attending physician to privately discuss with the individual whether he is feeling coerced or unduly influenced by any others before prescribing an aid-in-dying drug. By definition, this would mean if the patient is in the presence of any other person, then the attending physician must insist or require a private one-on-one conversation with the patient outside the presence of others, even if the patient protests.

Clearly, these arduous requirements are intended to protect the qualified individual from being pressured into a decision to obtain an aid-in-dying drug and terminate his or her life by anyone who stands to receive any personal financial benefit upon the death of the individual or by anyone who simply wants to avoid the expense of routine care and palliative treatment during the patient’s last days.

### How to Transact and Dispense the Aid-In-Dying Drug

Medications used for aid-in-dying purposes may include secobarbital and pentobarbital, both Schedule II controlled substances. As such, the pharmacist receiving these prescriptions must ensure that the prescription order is submitted on a secure tamper-resistant prescription form with the required security features and that it has been executed by the attending physician in accordance with the law. The Act permits the pharmacist to receive such prescriptions via hard copy by mail or personally delivered by the attending physician, or via properly authenticated e-prescribing. However, there is a distinct procedural difference between processing an aid-in-dying prescription order and a typical outpatient/community C-II prescription. An aid-in-dying drug prescription order must be delivered directly via those specified means from the attending physician to the pharmacist. An aid-in-dying prescription itself will never be handed to the qualified individual himself (nor his agent). In other words, the pharmacist should never be presented with prescription orders for aid-in-dying drugs by the qualified individual or his or her agent.

According to the Act, the pharmacist may dispense an aid-in-dying drug directly to the qualified individual, or deliver the completed prescription order for an aid-in-dying drug to the attending physician or a person expressly predesignated by the qualified individual to the pharmacist via a written or verbal authorization. Alternatively, the completed prescription order may be delivered via messenger service or mail/commercial carrier (signature required) to the attending physician, the qualified individual, or to any person predesignated by the qualified individual.

Interestingly, a conflict of law exists between the Act, which is a California state law, and the Drug Enforcement Agency’s interpretation of “constructive transfer” under the federal
Controlled Substance Act ("CSA"). The DEA suggests that a pharmacist delivering a completed prescription order for an aid-in-dying drug to the attending physician’s office for subsequent delivery to the qualified individual violates the CSA because of its explicit definitions for the terms "dispense," "deliver," and "ultimate user," as follows:

- **Under § 11010**, the term "dispense" means "to deliver a controlled substance to an ultimate user...pursuant to the lawful order of a practitioner, including the prescribing, furnishing, packaging, labeling, or compounding necessary to prepare the substance for that delivery."
- **Under § 11009**, the term "deliver" means "the actual, constructive, or attempted transfer from one person to another of a controlled substance, whether or not there is an agency relationship."
- **Under § 11030**, the term "ultimate user" means "a person who lawfully possesses a controlled substance for his own use or for the use of a member of his household or for administering to an animal owned by him or by a member of his household."

These terms of the Controlled Substances Act had not been interpreted judicially nor explained by the DEA until the case of Wedgewood Village Pharmacy v. DEA, which resulted in a 2010 stipulated settlement between the DEA and the Wedgewood Village Pharmacy ("Wedgewood"). In the DEA’s "Administrative Memorandum of Agreement" ("Agreement") with Wedgewood, the agency clearly opined on the intended meaning of the term "constructive transfer" and how it applies to whether a pharmacy is permitted to deliver a completed controlled substance prescription order to a prescriber, even where that prescriber is the ultimate user’s (i.e., the patient’s) physician. DEA terms and conditions in that agreement stated:

> "The DEA’s core legal position has been and remains that the transfer of a controlled substance to anyone (including the prescribing practitioner) other than an ‘ultimate user’ as that term is defined in the CSA [Controlled Substances Act] constitutes the distribution of a controlled substance...[and drug distribution is not allowed by pharmacies – only dispensing]."

(Wedgewood v. DEA, 509 F.3d 541: See DEA Administrative Memorandum of Agreement, page 3, Paragraph II)

Based on the principles outlined by the DEA in the Wedgewood case, a pharmacist choosing to participate within the parameters of the Act should explain to the attending physician the specific options for delivery of the aid-in-dying drug to the qualified individual permitted under the Act and emphasize that the DEA’s definition for "constructive transfer" would not allow delivery of completed prescription orders for aid-in-dying drugs (to the extent they are controlled substances) directly to the attending physician.

Even after a qualified individual has completed the requirements under the Act, another substantial hurdle must be overcome to obtain the aid-in-dying drug, and that is the potentially prohibitive cost of these medications. Lexicomp\textsuperscript{TM} estimates the cash price of Seconal\textsuperscript{TM} 100 mg #90 at $3,329.16, an expense that many patients may have to pay out of pocket.\textsuperscript{12} While Medi-Cal, California’s state Medicaid program, covers aid-in-dying drugs when all of the Act’s requirements are met,\textsuperscript{13} private insurers are not legally compelled to offer the same. This noteworthy financial burden may therefore prevent individuals who may be legally qualified to obtain aid-in-dying drugs from doing so.

Separately, pharmacists who contemplate compounding aid-in-dying drugs pursuant to patient-specific prescriptions would be well advised to prepare for the newly created rigors imposed on hazardous compounding under the United States Pharmacopeia (USP), Chapter 800 in its new General Chapter 800 ("USP 800"), as well as all of the new California State Board of Pharmacy hazardous compounding regulations that took effect January 1, 2017.

**Consultation with Qualified Individuals for Aid-In-Dying Drugs**

The Act does not impose any affirmative duty on pharmacists to provide any special patient consultation when dispensing aid-in-dying drugs to qualified individuals. In fact, because the Act is completely silent on pharmacist consultation, pharmacists should refer to the standard requirements set forth in California Code of Regulations § 1707.2(a)\textsuperscript{14} and § 1707.2(c)\textsuperscript{15}. However, pharmacists should understand and appreciate the rigorous mandatory consultation required by the Act by attending physicians before any prescription orders for aid-in-dying drugs are written. Specifically, an individual seeking aid-in-dying drugs must be personally counseled by the attending physician on all of the following:\textsuperscript{16}

1. Arranging to have another person present when ingesting the aid-in-dying drug;
2. Making sure not to ingest the aid-in-dying drug in a public place;\textsuperscript{17}
3. Considering notifying next of kin, but that eligibility to receive the aid-in-dying drug does not depend on such notification;
4. Considering participating in a hospice program;
5. Ensuring storage of the aid-in-dying drug in a safe and secure location until the time of ingestion, if ever; and
6. Understanding that he may withdraw or rescind his request for an aid-in-dying drug at any time and in any manner.

Since the attending physician must cover the above subject matter with the qualified individual through an in-person
CPhA partnered with the National Association of Chain Drug Stores (NACDS) to develop the Advanced Practice Pharmacist certificate program that satisfies 4210(a)(2)(A): “Earn certification in a relevant area of practice...”. This certificate program provides pharmacists with the knowledge and skills to expand their scope of practice as an advanced practice pharmacist.

The program consists of five modules reviewing patient assessment, ordering and interpreting drug therapy related tests, patient referral, drug therapy management, and documentation.

The APP certificate program consists of three components:

- 30 hours (3.0 CEU) self-study modules with assessment exam
- 8.0 hour (0.80 CEU) live seminar with interactive case studies and hands on assessment
- Comprehensive final examination

By successfully completing this program, the candidate will receive a certificate which will satisfy section 4210(a)(2)(A), one of two criteria required to become an advanced practice pharmacist (APP). Visit www.apppharmacist.com to learn more!

what are the benefits of becoming an APP?

Successful candidates who meet two of the three criteria and apply with the California State Board of Pharmacy to become an APP are authorized to:

- Perform patient assessments
- Order and interpret drug therapy-related tests in coordination with a patient’s primary care provider or diagnosing prescriber to monitor patient progress
- Refer patients to other health care providers
- Participate in the evaluation and management of diseases and health conditions in collaboration with other health care providers
- In accordance with a protocol with a physician or facility, a pharmacist may initiate, adjust, and discontinue drug therapy upon referral from a patient’s treating prescriber when necessary and medically appropriate
background

The California Pharmacists Association (CPhA) spearheaded a bill also known as SB 493 signed by Governor Jerry Brown on October 1, 2013. This bill not only recognizes pharmacists as health care providers, but also develops a new classification known as the advanced practice pharmacist.

what is an advanced practice pharmacist?

According to the California State Board of Pharmacy’s website, “An advanced practice pharmacist is a licensed pharmacist who has been recognized by the board, pursuant to Section 4210. A board-recognized advanced practice pharmacist is entitled to practice advanced practice pharmacy, as described in Section 4052.6, within or outside of a licensed pharmacy. The advanced practice pharmacist license shall be coterminal with the licensee’s pharmacist license.”

what are the requirements?

The new statute states that in order for a pharmacist to be recognized by the California Board of Pharmacy as an advanced practice pharmacist, you must satisfy at least two of the following:

1. **4210(a)(2)(A):**
   “Earn certification in a relevant area of practice, including, but not limited to, ambulatory care, critical care, geriatric pharmacy, nuclear pharmacy, nutrition support pharmacy, oncology pharmacy, pediatric pharmacy, pharmacotherapy, or psychiatric pharmacy, from an organization recognized by [ACPE] or another entity recognized by the board.”

2. **4210(a)(2)(B):**
   “Complete a postgraduate residency through an accredited postgraduate institution where at least 50 percent of the experience includes the provision of direct patient care services with interdisciplinary teams.”

3. **4210(a)(2)(C):**
   “Have provided clinical services to patients for at least one year under a collaborative practice agreement or protocol with a physician, advanced practice pharmacist, pharmacist practicing collaborative drug therapy management, or health system.”
consultation prior to ordering an aid-in-dying drug, pharmacists should avoid redundant patient consultation at the point of dispensing and, rather, counsel the qualified individual about the mechanics and anticipated side effects that the individual may encounter. The role of the pharmacist when interacting with the patient at this point should be to provide clear instructions and guidance on how to properly self-administer the Aid-in-dying drug and what to reasonably expect. For example, patient instructions could include:

1. How to carefully open each capsule and pour out the capsule’s entire contents without spillage or waste;
2. Which beverages may be considered, as well as which should be avoided;
3. What the proper sequence and timing are for ingestion of the aid-in-dying drugs;
4. Within what optimal period of time must full ingestion of the entire dose be completed;
5. What the relevant side effects are of not only the aid-in-dying drug, but also any previously ingested antinausea and/or antiemetic pretreatment(s);
6. What to do if the patient changes his mind in the middle of or immediately after the process of ingesting the aid-in-dying drug;
7. What the patient should do if the aid-in-dying drug does not work; and
8. How to properly destroy unused drugs if, at any time, the patient aborts the process because he changed his mind or died before the aid-in-dying drug was ever used.

Compliance, Liability, and Discretion to Not Participate in the Act

It is equally important for the pharmacist to have a high degree of confidence that the attending physician completed all procedural requirements under the Act. To provide some measure of assurance, the pharmacist should request a copy of the patient’s completed and executed request for the aid-in-dying drug document from the attending physician, and then keep that copy on file with the original prescription order. The pharmacist in charge should implement clear and unambiguous policies and procedures to avoid violating the Act and corresponding new sections of the California Health and Safety Code, and also to provide for some measure of consistency in pharmacist consultations with a qualified individual.

Participation in the Act by any healthcare provider, whether that provider is an attending physician or a pharmacist, is purely optional, discretionary, and arbitrary. No language prohibits or requires any healthcare provider to participate in any aspect of the Act. In fact, the Act itself provides absolute immunity for healthcare providers from any form of retaliation and liability. Specifically, healthcare providers are given immunity from any civil, criminal, administrative, disciplinary, employment, or credentialing proceedings as well as from any contractual liability. In addition, the Act prohibits a healthcare provider or professional organization from subjecting a provider to censure, discipline, suspension, loss of license, loss of privileges, loss of membership, or any other penalty for participating in good faith compliance or for refusing to participate in an End of Life Option Act request. In summary, a healthcare provider has the freedom to choose whether or not to participate in the Act, and as long as the provider complies with all of the regulations set forth, the law provides full protection from any liability, discipline, and other negative consequences.

However, the robust shield from liability described for a provider’s good faith compliance does not apply in the case of a provider who chooses to participate and fails to comply with the strict terms of the Act. That is precisely why pharmacists must have a high degree of confidence in the attending physician, as well as his or her working knowledge of the Act, and ensure that all of the technical requirements of the Act have been indisputably satisfied.

Conclusion

The End of Life Option Act permits pharmacists to work with attending physicians to provide aid-in-dying drugs for the purpose of allowing qualified individuals an option and a means to end his or her own life on his or her own terms. In return, the Act unambiguously provides blanket immunity from any retaliation in any form, and even affords immunity to those who choose not participate. Pharmacists who choose to participate should do so only after fully understanding the requirements of the Act, appreciating the plight of the would-be qualified individual, and considering other laws and governmental agencies that speak to dispensing controlled substances.

About the Author

Tony J. Park, Pharm.D., J.D., brings unique insight and expertise based on his vast former experiences: as pharmacy manager of a chain drug store, as owner of multiple pharmacy-related businesses including an independent Hispanic pharmacy, home care company, secondary wholesaler, billing & reimbursement agency service, home nursing agency service, and closed-door pharmacy. He was also owner and Pharmacist-In-Charge of a compounding-only pharmacy licensed as one of the first “licensed sterile compounding” facilities in California. He is also currently a legislative advocate, an adjunct professor of pharmacy law and ethics, and a pharmacy continuing education speaker.

As one of the very few Pharmacist-Attorneys in California, Tony J. Park, Pharm.D., J.D. represents clients against state and
federal agency enforcement actions, educates individuals about changes and developments in healthcare law, and consults new and existing businesses about current and future opportunities in healthcare.

Resources for Healthcare Providers and Patients

The California Department of Public Health provides, on its website, valuable resources, including the text of the law itself, a number of provider forms, and a number of patient forms.21

- Physician Forms
  - Attending Physician’s Checklist & Compliance Form
  - Consulting Physician’s Compliance Form
  - Attending Physician’s Follow-up Form
  - What Forms Does the Attending Physician Have to Submit to CDPH?
- Patient Forms
  - Patient’s Request for Aid-In-Dying Drug
  - Final Attestation for Aid-In-Dying Drug
  - Interpreter’s Declaration

References


2. It is this author’s professional opinion that self-administration of an aid-in-dying drug through the use of one’s feeding tube will likely pass muster under the Act’s definition of “self-administer.”

3. As defined in the Act as “an incurable and irreversible disease that has been medically confirmed and will, within reasonable medical judgment, result in death within six months.” [Emphasis added]. HSC § 443.1(q).

4. HSC § 443.1(i)

5. HSC § 443.3(a)

6. HSC § 443.3(a) - (d)

7. HSC § 443.5(a)


9. HSC §11162.1

10. HSC § 443.5(b)-(c)

11. Wedgewood v. DEA, 509 F.3d 541.


14. (a) A pharmacist shall provide oral consultation to his or her patient or the patient’s agent in all care settings: (1) upon request; or (2) whenever the pharmacist deems it warranted in the exercise of his or her professional judgment. (b)(1) In addition to the obligation to consult set forth in subsection (a), a pharmacist shall provide oral consultation to his or her patient or the patient’s agent in any care setting in which the patient or agent is present: (A) whenever the prescription drug has not previously been dispensed to a patient; or (B) whenever a prescription drug not previously dispensed to a patient in the same dosage form, strength or with the same written directions is dispensed by the pharmacy.

15. (c) When oral consultation is provided, it shall include at least the following: (1) directions for use and storage and the importance of compliance with directions; and (2) precautions and relevant warnings, including common severe side or adverse effects or interactions that may be encountered.

16. HSC § 443.5(a)

17. HSC § 443.1(n): “Public place’ means any street, alley, park, public building, any place of business or assembly open to or frequented by the public, and any other place that is open to the public view or to which the public has access.”

18. HSC § 443.11; please see enclosed form marked “Request For An Aid-In-Dying Drug To End My Life In A Humane And Dignified Manner,” also downloadable from The Medical Board of California at: http://www.mbc.ca.gov/Forms/Licensees/aid-in-dying_request.pdf.

19. HSC § 443.14(c)

20. HSC § 443.14(b), § 443.14(e)(2)

REQUEST FOR AN AID-IN-DYING DRUG TO END MY LIFE IN A HUMANE AND DIGNIFIED MANNER

I, ________________________________________________________________,
am an adult of sound mind and a resident of the State of California.

I am suffering from ____________________________________________,
which my attending physician has determined is in its terminal phase and which has been medically confirmed.

I have been fully informed of my diagnosis and prognosis, the nature of the aid-in-dying drug to be prescribed and potential associated risks, the expected result, and the feasible alternatives or additional treatment options, including comfort care, hospice care, palliative care, and pain control.

I request that my attending physician prescribe an aid-in-dying drug that will end my life in a humane and dignified manner if I choose to take it, and I authorize my attending physician to contact any pharmacist about my request.

INITIAL ONE:

_____ I have informed one or more members of my family of my decision and taken their opinions into consideration.

_____ I have decided not to inform my family of my decision.

_____ I have no family to inform of my decision.

I understand that I have the right to withdraw or rescind this request at any time.

I understand the full import of this request and I expect to die if I take the aid-in-dying drug to be prescribed. My attending physician has counseled me about the possibility that my death may not be immediately upon the consumption of the drug.

I make this request voluntarily, without reservation, and without being coerced.

Signed: ___________________________________________ Dated: _______________

DECLARATION OF WITNESSES

We declare that the person signing this request:

(a) is personally known to us or has provided proof of identity;
(b) voluntarily signed this request in our presence;
(c) is an individual whom we believe to be of sound mind and not under duress, fraud, or undue influence; and
(d) is not an individual for whom either of us is the attending physician, consulting physician, or mental health specialist.

Witness 1: _______________________________ Date: _______________

Witness 2: _______________________________ Date: _______________

NOTE: Only one of the two witnesses may be a relative (by blood, marriage, registered domestic partnership, or adoption) of the person signing this request or be entitled to a portion of the person’s estate upon death. Only one of the two witnesses may own, operate, or be employed at a health care facility where the person is a patient or resident.
DNA to Diagnosis to Treatment…
A Dependent Paradigm

Craig S. Stern, RPh, PharmD, MBA, FASCP, FASHP, FICA, FLMI, FAMCP, FCPhA, CSP

“The scientific man does not aim at an immediate result. He does not expect that his advanced ideas will be readily taken up. His work is like that of the planter – for the future. His duty is to lay the foundation for those who are to come, and point the way.”

Nikola Tesla – physicist, engineer and inventor

In the hierarchy of health care prevention is the best. Diagnosis leading to intervention before complications is next best. Intervention by surgery, radiology, and medications to treat the problem is last best. From a benefit perspective, medication therapy has become the primary treatment modality in the ambulatory setting, shifting acute care toward a higher severity patient population. Medication therapy has moved towards targeted impacts on patient conditions with a growing emphasis on improved measures and analytics to refine diagnosis and target outcomes.

The technology exists to target and monitor many therapies to defined metrics such as blood metrics, medication blood levels, respiratory parameters, blood pressure, etc. Analytical techniques also exist to refine medication dosages and monitoring parameters to achieve improved outcomes at lower risk. DNA testing adds another dimension to the techniques available. While DNA testing is not applicable for all diseases and therapies it has generated a separate discipline of “precision medicine.”

Genomics has allowed for improved diagnostics such that diagnoses can be further refined into subsets of populations that are treatable with new and improved therapies. The therapies, commonly called “Specialty Medications,” target these subpopulations with a greater chance of success in cure or stabilization of the disease. Marrying diagnostics with therapy is the next evolutionary opportunity for professionals with extensive training in therapeutics.

This article will discuss the marriage of genetic and genomic testing with medications and its impact on providers. This is a review for providers and is not an exhaustive review of the literature.

The Situation

DNA testing is a relatively new area that is based on scientific principles and will evolve as more and better tests, as well as better medications, are introduced. The field currently has different terms to describe DNA testing. One option that has been published is that genetic testing is a diagnostic mindset that refers to screening large populations to determine who is susceptible to certain illnesses. Alternatively, genomic testing is a treatment mindset that refers to the treatment of a particular illness that will improve the outcome. Clearly, both types of testing require a consideration of the cost-effectiveness of doing any testing to ensure that there is a benefit beyond cost.¹

DNA Genomics

Deoxyribonucleic acid (DNA) is a molecule that carries most of the genetic instructions used in the growth, development, functioning and reproduction of almost all known organisms. It makes each species unique. DNA is found in the cell nucleus (nuclear DNA) and in the mitochondria (mitochondrial DNA). DNA is composed of four chemical base pairs: adenine (A), guanine (G), cytosine (C), and thymine (T). There are about three billion base pairs in the human body of which 99 percent are the same in all humans. The sequence of these bases determines the information used to provide the genetic instructions for each human. Each base is also attached to a sugar and a phosphate molecule. The base plus the sugar plus the phosphate molecules form a nucleotide. The nucleotides form the spiral double helix, which can be viewed as a ladder with the base pairs forming the rungs and the sugar and phosphate molecules forming the sidepieces. (Figure 1)

Mutations or changes to base pairs, about 1 in every 1300 base pairs, create gene variations that impact pharmacodynamics, drug responses and pharmacokinetics. A mutation is usually signified by an asterisk “*” within the name of the gene. Variations are known as “alleles.”
Basic Science Principles: Pharmacogenomics

Pharmacogenomics, also pharmacogenetics, is the study of genetic variations that influence an individual’s response to specific medications. Knowing that a patient carries a particular genetic variation (i.e., allele) helps prescribers to individualize medication therapy, decrease the probability of adverse events, and increase the effectiveness of the prescribed medication. Pharmacogenomics is composed of pharmacology (the science of how medications work) with genomics (the science of the human genome).

Pharmacogenomics targets medication activity to DNA variations in the human genome. Variations in the human genome are called “single nucleotide polymorphisms (SNPs).” There are approximately 11 million SNPs in the human population, averaging one every 1300 base pairs. Variant forms of a gene (alleles) usually arise due to mutations. Many genes have different forms which are located at the same position, i.e. genetic locus, on a chromosome. Humans have two alleles at each genetic locus with one allele inherited from each parent. Susceptibility to certain diseases and individual responses to particular drugs are linked to these SNPs. The science of pharmacogenomics, then, targets defective structural proteins that increase susceptibility to disease, and the genes that encode metabolic enzymes that alter a medication’s activity.  

Diagnoses from Genetic Testing

Each person would need to have the same specific pharmacogenomic test only once because a person’s genetic makeup does not change over time. However, one may need other pharmacogenomics tests if one takes another medication. Each medication is associated with a different pharmacogenomics test. The results of all genomic test results are stored with all laboratory tests to be used by health care providers.

There are several general approaches to selecting the patient in need of a biomarker or genetic test –

- Patient: Select a test based on a patient who is not responding to standard therapies
- Medication: Select a test based on a target medication
- Disease/Condition: Select a test based on a well-established relationship between the medication and a variant allele

The treating health care practitioner must decide, but pharmacists and other health care professionals have the responsibility to bring the issue up by counseling that includes the appropriate decision algorithm. Why is a test necessary? What is the published evidence to support a test? What will we do with the results? Can we achieve the same result by other, less costly means?

Treatment Based on Genomic Testing

There are at least one hundred genomic tests paired to specific medications and the number is increasing annually. Warfarin is often cited as the classic medication that is affected by the presence of variant alleles that reduce its rate of clearance from the body. Specifically, warfarin metabolism is encoded by the CYP2C9 gene among others. Variant alleles, e.g., CYP2C9*2 and CYP2C9*3, present in a patient reduce the metabolism of Warfarin, leading to higher concentrations of the medication in the body. As a result, patients with at least one copy of these alleles require a lower dose of Warfarin than do patients who are homozygous for the CYP2C9*1 allele. In addition, Warfarin works by inhibiting vitamin K-dependent clotting factors. The VKORC1 gene codes the vitamin K epoxide reductase enzyme, which is the Warfarin target. If a patient carries the -1639G>A polymorphism in a particular region of the VKORC1 gene, the so-called promotor region, then these patients are more sensitive to Warfarin and require lower doses. Therefore, a patient’s CYP2C9 and VKORC1 genotype can be used to determine the optimal starting dose of Warfarin.
Examples of other allele / medication pairings are:

- Patients infected with the HIV virus may receive an antiviral medication abacavir (Ziagen®). This therapy may lead to adverse drug reactions if the patient has a genetic variant. These patients are HLA-B*5701 allele carriers.

- Patients with breast cancer may be given trastuzumab (Herceptin®). This medication only works for patients with an overproduction of a protein known as HER2. As a result, physicians test for ERBB2 overproduction before providing trastuzumab.

- Patients with acute lymphoblastic leukemia may be given mercaptopurine (Purinethol®). Some patients cannot process this medication due to a genetic variation, TPMT, that leads to intermediate or poor metabolizers. The result is severe side effects as well as increased risk of infections. If the standard dose is adjusted, then the risk of these processing problems is significantly reduced.

- Patients with colon cancer may receive combination chemotherapy regimens containing irinotecan (Camptosar®). Some patients have a particular genetic variant that prevents them from clearing the medication resulting in severe diarrhea and increased risk of infections. These patients are UGTIA1*28 allele carriers. They require lower doses of the medication.

There are many more medications that are currently being researched. For example, clopidogrel (Plavix®) is a blood thinner used to reduce blood clots especially after PCI cardiac stents. Certain genetic variants may cause the medication to be ineffective as for example, Omeprazole. Also, gefitinib (Iressa®) and erlotinib (Tarceva®) may be more effective in patients with lung cancer when they have a specific genetic allele. However, cetuximab (Erbitux®) and panitumumab ( Vectibix®) do not work well in about 40% of colon cancer patients with a particular

### Table 1. Mature Medication Genetic Testing Examples

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Gene</th>
<th>Reference Subgroup</th>
<th>Action</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>ESR1, PGR</td>
<td>Hormone receptor positive</td>
<td>Positive</td>
<td>88360</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>TPMT</td>
<td>TPMT intermediate or poor metabolizers</td>
<td>Negative</td>
<td>81401</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B</td>
<td>HLA-B*1502 allele carriers</td>
<td>Negative</td>
<td>81380</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-A</td>
<td>HLA-A*3101 allele carriers</td>
<td>Negative</td>
<td>81380</td>
</tr>
<tr>
<td>Peginterferon alfa-2b</td>
<td>IFNL3</td>
<td>IL28B rs12979860 T allele carriers</td>
<td>Positive</td>
<td>81400</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>HLA-B</td>
<td>HLA-B*1502 allele carriers</td>
<td>Negative</td>
<td>81380</td>
</tr>
<tr>
<td>Rifampin, Isoniazid, and Pyrazinamide</td>
<td>NAT1-2</td>
<td>slow inactivators</td>
<td>Negative</td>
<td>81479</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>PML/R ARA</td>
<td>PML/RAR_alpha ((t(15;17)) gene expression positive</td>
<td>Positive</td>
<td>81315</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>POLG</td>
<td>POLG mutation positive</td>
<td>Negative</td>
<td>81406</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>NAGS, CPS1, ASS1, OTC, ASL, ABL2</td>
<td>Urea cycle enzyme deficient</td>
<td>Negative</td>
<td>81405</td>
</tr>
<tr>
<td>Warfarin</td>
<td>VKOR C1</td>
<td>VKORC1 rs9923231 A allele carriers</td>
<td>Negative</td>
<td>81355</td>
</tr>
<tr>
<td>Warfarin</td>
<td>PROC</td>
<td>Protein C deficient</td>
<td>Negative</td>
<td>85302</td>
</tr>
</tbody>
</table>

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The Alliance of Medication Safety (APMS) is a federally listed Patient Safety Organization (PSO).
Mental health, especially depression, is also a current target. Treatment requires weeks of therapy to determine if the medication will be effective, and if not, then another medication must be used. Selective serotonin receptor inhibitors (SSRIs) are a standard of therapy. Clinical trials are underway to identify genetic alleles that predict SSRI responsiveness. One example is that current studies indicate that patients on citalopram (Celexa®) are influenced by specific genetic variations. If these studies are validated, then there will be genetic variations for testing before administering SSRI antidepressants.

Ordering Genetic Tests

The volume of genetic tests (biomarkers) is increasing annually. As a result, medical specialists must focus on medications applicable to their specialty. To assist, the FDA has provided physicians, pharmacists and other generalists with some guidance. The Food and Drug Administration (FDA) requires/recommends information on genotyping drugs with their complementary biomarkers. FDA recommendations are listed in Table 2.

In addition to the FDA table, the Stanford University School of Medicine PharmGKB group provides tables to summarize good and bad news for drug interactions, side effects and dosing from genetic testing. These tables offer a level of information that clinicians may use to order genetic testing for prospective management of drug interactions and for confirmatory purposes. (Tables 3, 4)

Pharmacogenomics and New Drug Development

Pharmacogenomics offers an opportunity to improve the targeting of existing medications to the patient population that can benefit the most. The goal is to produce new drugs that are highly effective and do not cause serious side effects.

Different from traditional drug development that involves screening for medications with broad action against a disease, researchers

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>BIOMARKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine (Imuran®)</td>
<td>TPMT deficiency</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol®)</td>
<td>HLA-B*5101</td>
</tr>
<tr>
<td>Celecoxib (Celebrex®)</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>EGF receptor</td>
</tr>
<tr>
<td>Gefitinib (Iressa®)</td>
<td>EGF receptor mutations</td>
</tr>
<tr>
<td>Imatinib mesylate (Gleevec®)</td>
<td>C-kit mutations, BCR/ABL translocation</td>
</tr>
<tr>
<td>Irinotecan (Camptosar®)</td>
<td>UGT1A1, homozygous for the *28 allele</td>
</tr>
<tr>
<td>Maraviroc (Selzentry®)</td>
<td>HIV-CCR5 receptor site</td>
</tr>
<tr>
<td>Mercaptopurine (Purinethol)</td>
<td>TPMT deficiency</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>HER2-neu</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>CYP2C9; VKOR</td>
</tr>
</tbody>
</table>

Table 2. FDA Recommended List of Biomarkers

JAPhA, 51:6, Nov/Dec 2011, e71
Table 3. Summary of Genetic Good News – Stanford University

<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary</th>
<th>Level of Evidence</th>
<th>PMID</th>
<th>Gene</th>
<th>rsID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel; CYP2C19</td>
<td>CYP2C19 poor metabolizer, many drugs may need adjustment.</td>
<td>High</td>
<td>19106084</td>
<td>CYP2C19</td>
<td>rs4244285</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Requires lower dose</td>
<td>High</td>
<td>15888487</td>
<td>VKORC1</td>
<td>rs9923231</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Requires lower dose</td>
<td>High</td>
<td>19270263</td>
<td>CYP4F2</td>
<td>rs2108622</td>
</tr>
<tr>
<td>Metformin</td>
<td>Less likely to respond</td>
<td>Medium</td>
<td>18544707</td>
<td>CDKN2A/B</td>
<td>rs10811661</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Less likely to respond</td>
<td>Medium</td>
<td>18544707</td>
<td>CDKN2A/B</td>
<td>rs10811661</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Increased risk of nephrotoxicity</td>
<td>Low</td>
<td>19625999</td>
<td>SLC22A2</td>
<td>rs316019</td>
</tr>
<tr>
<td>Citralopram</td>
<td>May increase risk of suicidal ideation during therapy</td>
<td>Low</td>
<td>17898344</td>
<td>GRIA3</td>
<td>rs4825476</td>
</tr>
<tr>
<td>Escitalopram; Nortriptyline</td>
<td>Depression may not respond as well during therapy</td>
<td>Low</td>
<td>19365399</td>
<td>NR3C1</td>
<td>rs10482633</td>
</tr>
<tr>
<td>Morphine</td>
<td>May require higher dose for pain relief</td>
<td>Low</td>
<td>17156920</td>
<td>COMT</td>
<td>rs4680</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Cancer may respond less well</td>
<td>Low</td>
<td>18836089</td>
<td>ABCB1</td>
<td>rs1045642</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>May require higher dose</td>
<td>Low</td>
<td>15116054</td>
<td>SLC01B1</td>
<td>rs2306283</td>
</tr>
<tr>
<td>Talinolol</td>
<td>May require higher dose</td>
<td>Low</td>
<td>18334920</td>
<td>ABCC2</td>
<td>rs2273697</td>
</tr>
</tbody>
</table>

PharmGKB, http://www.pharmgkb.org/

Table 4. Summary of Pharmacogenetic Bad News – Stanford University

<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary</th>
<th>Level of Evidence</th>
<th>PMID</th>
<th>Gene</th>
<th>rsID</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG COA Reductase</td>
<td>No increased risk of myopathy</td>
<td>High</td>
<td>18650507</td>
<td>SLCO1B1</td>
<td>rs4149056</td>
</tr>
<tr>
<td>Statins</td>
<td>No increased risk of myopathy</td>
<td>High</td>
<td>12811365</td>
<td>SLCO1B1</td>
<td>rs4149056</td>
</tr>
<tr>
<td>Desipramine; Fluoxetine</td>
<td>Depression may improve more than average</td>
<td>Medium</td>
<td>19414708</td>
<td>BDNF</td>
<td>rs1888800</td>
</tr>
<tr>
<td>Fluavastatin</td>
<td>Good response</td>
<td>Medium</td>
<td>18781850</td>
<td>SLCO1B1</td>
<td>rs11045819</td>
</tr>
<tr>
<td>Metoprolol and other</td>
<td>Normal CYP2D6 metabolizer.</td>
<td>Medium</td>
<td>19037197</td>
<td>CYP2D6</td>
<td>rs38820971/180076</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>May have good response</td>
<td>Medium</td>
<td>15199031</td>
<td>HMGC1</td>
<td>rs1723540</td>
</tr>
<tr>
<td>Pravastatin, Simvastatin</td>
<td>No reduced efficacy</td>
<td>Medium</td>
<td>15199031</td>
<td>HMGC1</td>
<td>rs17244414</td>
</tr>
<tr>
<td>Caffeine</td>
<td>No increased risk of heart problems with caffeine</td>
<td>Low</td>
<td>16522833</td>
<td>CYP1A2</td>
<td>rs762551</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>No increased risk of heart problems with caffeine</td>
<td>Low</td>
<td>15522280</td>
<td>KCNH2</td>
<td>rs36210421</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>SNP is part of protective haplotype for hypersensitivity to carbamazepine</td>
<td>Low</td>
<td>16538175</td>
<td>HSPA1A</td>
<td>rs1043620</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Reduced risk of hepatotoxicity</td>
<td>Low</td>
<td>16912956</td>
<td>ABCB1</td>
<td>rs1045642</td>
</tr>
<tr>
<td>Efavirenz; Nevirapine</td>
<td>Reduced risk of hepatotoxicity</td>
<td>Low</td>
<td>16912956</td>
<td>ABCB1</td>
<td>rs1045642</td>
</tr>
<tr>
<td>Epoetin Alfa</td>
<td>Lower dose of iron and epo required</td>
<td>Low</td>
<td>18025780</td>
<td>HFE</td>
<td>rs1799945</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Average blood levels expected</td>
<td>Low</td>
<td>11503014</td>
<td>ABCB1</td>
<td>rs1045642</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Irbesartan may work better than beta-blocker</td>
<td>Low</td>
<td>15453913</td>
<td>APOB</td>
<td>rs1367117</td>
</tr>
<tr>
<td>Lithium</td>
<td>Increased likelihood of response</td>
<td>Low</td>
<td>18408563</td>
<td>CACNG2</td>
<td>rs5750285</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>May have improved response</td>
<td>Low</td>
<td>17913323</td>
<td>ABCB1</td>
<td>rs2032582</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>More likely to respond</td>
<td>Low</td>
<td>19396436</td>
<td>DRD3</td>
<td>rs6280</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No reduced efficacy</td>
<td>Low</td>
<td>15226675</td>
<td>SLC01B1</td>
<td>rs1419015</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>May have good response</td>
<td>Low</td>
<td>18693052</td>
<td>APOB</td>
<td>rs10192566</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>No increased risk of apnea</td>
<td>Low</td>
<td>1415224</td>
<td>BCHE</td>
<td>rs2893389</td>
</tr>
</tbody>
</table>

PharmGKB, http://www.pharmgkb.org/

Notes: PMID is a unique number used to identify articles in PubMed. rsID stands for Reference SNP cluster ID. SNP, or single-nucleotide polymorphism, is the variation in a single nucleotide that occurs at a specific position in the genome. rsID is the accession number used by researchers and databases to refer to specific SNPs. When genome-wide association studies linking SNPs or traits to conditions are reported, they use the rsID for reference.
are now using genomic information to design drugs aimed at patients with specific genetic profiles. Researchers are also using pharmacogenomic tools to find drugs targeting specific molecular and cellular pathways involved in diseases.

For example, bucindolol (Gencaro), a beta-blocker to treat heart failure, was never marketed. However, after tests showed that the drug worked well in patients with two genetic variants that regulate heart function, there is renewed interest.

Cost-Benefit Issues

Marrying drugs to genetic biomarkers adds cost to health care. It is necessary to be sensitive to the value of a test versus the benefit derived from its use. As with all laboratory testing, genetic biomarkers have been studied to a greater or lesser degree and have established benefits limited by their specificity (true negatives) and sensitivity (true positives). Many references, including Lexicomp, reflect the evidence supporting testing with scoring criteria.7

The American Medical Association (AMA) has made the case that testing leads to cost savings for the overall healthcare system, by cost avoidance although not necessarily for each patient. The AMA cites:8

- Decreasing the number of adverse drug reactions
- Decreasing the number of failed drug trials
- Decreasing the time it takes to achieve drug approvals
- Decreasing the duration of therapy for specific medications
- Decreasing the number of medications to achieve an effective result
- Decreasing the effects of disease through early detection

Ultimately, the cost-benefit must be decided for each patient. The value equation is a result of the sum total of all interventions. As the science is new, it is incumbent on the entire health care team, including the patient, to identify, discuss and participate in the decision to utilize a pharmacogenomic test.

Conclusion

Tesla was right. Science takes time to integrate into clinical practice. Furthermore, the complexity of DNA knowledge integrated into clinical practice will require extensive training for current and future practitioners. As practitioners are trained in the benefits of pharmacogenomic testing, the practice will expand. It will be incumbent on all practitioners to understand the benefits of these tests on particular patients. Since the application of this knowledge requires experts in multi-specialities, the application of this knowledge fits well into a team approach. The science requires objectivity, and patients need this type of objective information in order to make more informed decisions. Pharmacists are in a unique position to select appropriate patients, offer guidance, education and monitoring for applicable medications. Pharmacogenomics and precision medication offers a new area for pharmacy practice that is both exciting and challenging.

About the Author

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New Laws That Expand The Role Of The Pharmacist In Patient Care

Fred G. Weissman, PharmD, JD; Ettie Rosenberg, PharmD, JD

Abstract
California Senate Bill 493 (SB 493), signed into law on October 1, 2013, marked the recognition of California pharmacists as health care providers, and also enumerated various authorities for pharmacists to provide direct health care services to patients. This article reviews the history of laws enacted which have afforded pharmacists opportunities to provide a variety of direct patient care services, and addresses the most recently implemented statewide protocols authorizing pharmacist involvement in direct patient care designated under SB 493.

Introduction
Over the last 30 years in California and throughout the country, our profession has witnessed an evolution of laws encouraging pharmacists to become more engaged in direct patient care responsibilities. One of the earliest, California Business and Professions Code Section 4103 (Cal. Bus. & Prof. Code § 4103) was introduced in the 1980s and authorized a pharmacist to take a patient’s blood pressure, to inform the patient whether the reading falls “within a high, low, or normal range,” and as necessary to advise the patient to consult their physician of choice. Section 4103 further requires a pharmacist who provides blood pressure services to use “commonly accepted community standards in rendering opinions and referring patients to physicians.”

In the early 1990s, Congress passed the federal Omnibus Budget Reconciliation Act of 1990 (OBRA '90), which for the first time advanced an expectation of pharmacists extending beyond simple oversight of drug distribution and including, or rather, requiring pharmacists to be involved in both detection and resolution of problems with drug therapy. As the first federal law to directly regulate the pharmacy profession, OBRA ’90 effectively changed the manner in which pharmacy would thereafter be practiced. Congress aimed to save the federal government money on its medication-related budget expenditures, because OBRA ’90 required states to establish standards of drug review and patient consultation in order to continue receiving federal funds for their Medicaid patients, thereby effectuating a direct impact on pharmacy practice.

OBRA ’90 laid the foundation for the pharmacist’s duty to provide patient consultation in California Code of Regulations Section 1707.2 (CCR § 1707.2) ("consultation law"). The duty to consult under CCR Section 1707.2 crossed the line from encouraging pharmacists to participate in direct patient care services to mandating their participation. CCR Section 1707.2 mandates a California pharmacist to provide verbal consultation to a patient under four circumstances: (1) whenever a new prescription has not been previously dispensed to that patient; (2) whenever a prescription drug has not been previously dispensed to a patient in the same dosage form, at the same strength, or with the same written directions; (3) whenever the pharmacist, in the exercise of his or her professional judgment, finds it necessary to consult with the patient; and (4) upon request by the patient. The duty to consult mandates that the patient be properly informed on (a) how to use the medication; (b) the importance of complying with the directions on the label; (c) how to store the medication; and (d) the common severe adverse drug actions and interactions.

Notably, when the consultation law first came into effect, a large contingent of practicing community pharmacists were unhappy because they believed that Section 1707.2 requirements directly interfered with the time required for pharmacists working in the community to complete their routine prescription processing workflow. Thus, community pharmacists initially viewed the law as a burden. Over time, however, the consultation law has become perhaps one of the most important patient care laws in existence, because it affords the pharmacist an opportunity to ensure that patients understand the importance of compliance, as well as the benefits and risks associated with the medications they use. The public at large has also come to recognize the value of the pharmacist’s consultation as a significant benefit to patients. In fact, patients generally appreciate, expect, and often
pursue the pharmacist’s expertise to serve their individual health care needs.

Subsequently, the reach of the consultation law under CCR Section 1707.2 was extended to include, in addition to patient consultation, new requirements for review and maintenance of individual patient medication profiles in CCR Sections 1707.1 and 1707.3, respectively (“medication profile law”). When properly followed, the medication profile law promotes comprehensive review of a patient’s past medication history in the context of a newly presented prescription, a review that is intended to ensure medication compliance and to facilitate detection of, and avoid any possible incompatibilities or drug interactions. A patient’s medication profile routinely contains historical information about their individual drug history and medical conditions or problems being treated, and thus serves as a platform for “drug utilization review” (DUR). A patient’s medication profile can also alert the pharmacist to potential allergies, contraindications, and even possible intentional or unintentional medication misuse and abuse patterns.

The early 1990s saw further “expanded scope of practice” laws with CCR Sections 4052.1 and 4052.2, which aimed specifically at appropriately trained pharmacists who practiced in licensed health operations such as, for example, skilled nursing facilities, where physicians were not readily available. Under the “expanded scope of practice,” a pharmacist working in specific practice contexts could perform specified patient care tasks pursuant to a designated prescriber’s (or prescriber-group’s) well-defined protocol. Sections 4052.1 and 4052.2 authorized a pharmacist practicing in those contexts to: a) order or perform routine drug therapy-related patient assessment procedures, including taking temperatures, pulse rates, and respiration measurements; b) order drug therapy-related laboratory tests; c) administer drugs and biologicals by injection; and d) initiate and adjust the drug regimens for a patient. Since that time, the expanded scope of practice has been extended to all types of pharmacy patient care venues (e.g., hospitals, community, and clinics) as long as there is a prescriber-directed protocol which supports it.

From a historical perspective, Sections 4052.1 and 4052 initially expanded the pharmacist’s scope of practice, opening the door for subsequent laws, and served as the springboard for introduction of California Senate Bill 493 (SB 493) in February 2013 by State Senator Ed Hernandez. Shortly thereafter, SB 493 passed in both the California Assembly and Senate and was ultimately signed into law by Governor Jerry Brown on October 1, 2013. For the first time in California, SB 493 recognized pharmacists as health care providers (hence the moniker “California provider status law”) with the authority to provide direct health care services to patients. A host of other laws enacted over the past 25 years have also afforded pharmacists opportunities to provide a variety of direct patient care services, including (a) performing skin punctures to test for glucose and cholesterol levels (Cal. Bus. Prof. Code § 4052.4); (b) providing immunizations (Cal. Bus. Prof. Code § 4052.8); (c) furnishing emergency contraceptive therapy (Cal. Bus. Prof. Code § 4052.3); (d) Cal. Bus. Prof. Code § 4052.3, the first of those authorities listed in SB 493, was enacted April 1, 2013, and followed by the protocols for emergency contraception in the California Code of Regulations § 1746 (CCR § 1746) implemented effective July 1, 2013.

Since the passage of SB 493, the California Board of Pharmacy has developed implementation regulations to support the expanded areas of pharmacist involvement in patient care designated under SB 493. This article provides a discussion of the recent laws allowing new opportunities for pharmacists who want to take the next steps required for any of the various expanded pharmacist patient care practices, such as (a) recognition as an Advanced Practice Pharmacist (APP) (Cal. Bus. & Prof. Code §§ 4210, 4052.6); (b) authority to continue to initiate and administer vaccines (Cal. Bus & Prof Code § 4052.8; CCR § 1746.4); (c) authority to furnish the drug naloxone for suspected opioid intoxication without a prescription (Cal. Bus, & Prof. Code § 4052.01; CCR § 1746.3); (d) authority to furnish hormonal contraception in addition to emergency oral contraception (CCR § 1746.1; Cal. Bus. & Prof. Code 4052.3); (e) authority to furnish nicotine replacement products (CCR § 1746.2); and/or (f) authority to furnish prescription travel medications which do not require a diagnosis and are recommended by the Centers for Disease Control and Prevention (CDC) for individuals traveling outside the United States (Cal. Bus. & Prof. Code § 4052.9; CCR § 1746.5).

The discussion below references provisions contained within California Business and Professions Code Chapter 9, Division 2, Article 3 on Scope of Practice and Exemptions, and Title 16 of the California Code of Regulations, Article 3.5 on Advanced Practice Pharmacist, Article 5 on Dangerous Drugs, and Article 6 on Fees.

**Advanced Practice Pharmacist Designation**

Advanced Practice Pharmacist (APP) status is a classification limited to licensed pharmacists recognized by the Board of Pharmacy as having the requisite training and skills to provide specifically defined direct patient care services within or outside of a licensed pharmacy. A board-recognized Advanced Practice Pharmacist may: (a) perform patient assessments; (b) order and interpret drug therapy-related tests; (c) administer vaccines and immunization products; (d) administer epinephrine or diphenhydramine by injection for the treatment of severe allergic reactions; (e) participate in the evaluation and management of diseases and health conditions in collaboration with other health care providers; and (f) initiate, adjust, or discontinue drug therapy as part of the evaluation and management of patients’ diseases and health conditions.
Licensure requirements for consideration as an Advanced Practice Pharmacist (APP) are found in Cal. Bus. & Prof. Code Section 4210, and effective December 13, 2016, APP certification, application, and fee requirements are found in Title 16, California Code of Regulations Sections 1730, 1730.1, and 1749; while effective August 10, 2016, criteria for APP certification programs are found in CCR Section 1730.2. Moreover, to apply for APP status, a pharmacist must have an active license in good standing with the California Board of Pharmacy and must meet at least two of the following requirements:

1. Possess certification in a relevant area of practice, including, but not limited to, ambulatory care, critical care, geriatric pharmacy, nuclear pharmacy, nutrition support pharmacy, oncology pharmacy, pediatric pharmacy, pharmacotherapy, or psychiatric pharmacy, from an organization recognized by the Accreditation Council for Pharmacy Education or another entity recognized by the board. (16)

2. Completed a postgraduate residency in the US through an accredited postgraduate institution where at least 50 percent of the experience includes the provision of direct patient care services with interdisciplinary teams. (16)

3. Provided clinical services to patients (within 10 years of application) for at least one year (1,500 hours) under a collaborative practice agreement or protocol with a physician, advanced practice pharmacist, pharmacist practicing collaborative drug therapy management, or health system, where such clinical experience included initiating, adjusting, modifying, or discontinuing drug therapy of patients. (16)

Certification as an Advanced Practice Pharmacist (APP) shall be valid for a two-year term which runs concurrent with the certificate holder's license to practice pharmacy in California. (17)

In addition to satisfying Cal. Bus. & Prof. Code Section 4210 (a) (2) and California Code of Regulations Sections 1730, 1730.2 (a) requirements, APP certification programs must also satisfy other criteria under Title 16, California Code of Regulations Sections 1730.2 (b) (1) through (5), which provide:

1. The certification program includes specified learning objectives in at least five sequentially ordered education modules covering the following topics: performing patient assessments; ordering and interpreting drug therapy-related tests; referring patients to other health care providers; participating in the evaluation and management of diseases and health conditions in collaboration with other health care providers; and initiating, adjusting, modifying, or discontinuing drug therapy.

2. The certification program requires assessment after completion of each of the education modules in an examination format or by other assessment methodology that confirms the participant's understanding, knowledge, and application of the specified learning objectives for the module, where any failure to successfully complete the assessment in any module prevents advancement to the next module.

3. The certification program requires that instruction and assessments in each of the modules are developed and provided by either an Advanced Practice Pharmacist licensed by the board or an expert with experience in the respective area(s) above who is qualified to teach at a school of pharmacy recognized by the board.

4. The certification program requires that, upon successful completion of all modules and their respective assessments, each participant shall earn a passing score on a final overall assessment before being awarded certification.

5. The certification program require(s) a minimum of 10 hours of continuing education on the topics identified above every two years to maintain certification. This is in addition to the 30 hours of continuing education required every two years. (19)

New Laws Promoting Direct Patient Care Services Delivered by Pharmacists

Pharmacists Initiating and Administering Vaccines

CCR Section 1746.4 provides the state protocol for and requires the pharmacist to be certified in: a) administering immunization products by an approved and accredited program; b) administering basic life support, and c) completion of two hours of continuing education every two years. Under CCR Section 1746.4, a pharmacist is responsible to maintain documentation of the patient’s vaccination, and to provide certain notifications, including to provide a copy of the vaccine administration record to the patient and to the patient’s primary care provider within 14 days of any vaccine administered; or alternatively, to enter the appropriate information in a patient record system shared with the primary care provider.

In addition, CCR Section 1746.4 requires the pharmacist to report the patient’s vaccination information to one or more state and/or local immunization information systems within 14 days of the administration of such vaccine and to inform the patient of the vaccine information shared with others.
Pharmacists Furnishing Naloxone Hydrochloride

CCR Section 1746.3, effective on January 27, 2016, provides the statewide protocol for pharmacists furnishing naloxone hydrochloride. CCR Section 1746.3 has a training requirement as well, and pursuant to Section 4052.01, authorizes the appropriately trained pharmacist to furnish naloxone hydrochloride to patients or others seeking help to treat or prevent an opioid overdose. Regardless of the dosage form furnished, whether injectable or nasal naloxone, pursuant to CCR Section 1746.3, the following conditions must be satisfied:

1. Training (a minimum of one hour of board-approved continuing education specific to the use of naloxone or an equivalent curriculum-based program completed in a school of pharmacy).

2. Screening each potential naloxone recipient with a series of standardized questions to ascertain the individual’s history of opioid use and any possible problems that might arise from the use of the opioid product.

3. Providing the naloxone recipient training in opioid overdose prevention, recognition, response, and administration of the antidote naloxone.

4. Providing the naloxone recipient with appropriate counseling and information regarding the naloxone, with the recipient not being allowed to waive the consultation.

5. Providing the naloxone recipient with informational resources involving referrals to where they may seek further help regarding addiction.

6. Providing the recipient’s physician notice of any drug or device furnished. If the recipient does not have a primary care provider or chooses not to give notification consent, then the pharmacist shall provide a written record of the naloxone issued to a health care provider the recipient chooses at a later date.

7. Maintaining documentation in a medication record for the naloxone recipient to be kept in the pharmacy for a three-year period.

8. Maintaining all recipients’ naloxone records in privacy, as will be noted in the pharmacy’s policy and procedures.

Pharmacists Furnishing Hormonal Contraception

As discussed above, an earlier provision, Cal. Bus. & Prof. Code Section 4052.3, previously authorized the pharmacist to furnish emergency oral contraceptives. Effective April 8, 2016, CCR Section 1746.1 authorizes a specially trained pharmacist to also furnish patients with monthly regimens of contraceptive agents. Similar to the other pharmacist-directed patient care protocols, requirements for furnishing self-administered hormonal contraception include:

1. Furnishing of a hormonal contraceptive agent must be in accordance with a protocol approved by the Board of Pharmacy and the Medical Board of California.

2. The hormonal contraceptive may be in a variety of dosage forms that include oral, transdermal, vaginal, or by depot injection.

3. Steps the pharmacist must follow when furnishing a contraceptive:
   a. Requiring the patient to complete a self-screening tool (22-response standardized questionnaire) and review the responses to gain insight about any potential negative history or current problems the patient may be experiencing that may possibly prevent the product from being furnished. If the patient is to be continued on the hormonal contraceptive agent, the patient must complete a new questionnaire each year, or whenever the patient indicates a major health change.
   b. Measuring and recording the patient’s seated blood pressure if combined hormonal contraceptives are requested or recommended.
   c. Ensuring that the patient is counseled and appropriately trained in the administration of the contraceptive drug.
   d. Providing the patient with a medication guide on hormonal contraceptives.

The self-screening tool completed by the patient, as well as other records concerning the individual furnished with a hormonal contraceptive, must be kept for a three-year period from the last entries on any such records. Based on answers to the self-screening survey, and further questioning of the patient, the pharmacist should determine whether it is appropriate to furnish or not furnish the hormonal contraceptive agent. If furnished, the pharmacist must notify the patient’s primary care provider that a contraceptive product was provided. In the event the patient does not have a primary care provider, the pharmacist must provide the patient with a written record of the contraceptive agent furnished, and advise the patient to consult with a health care provider of their choice. Selection of a specific hormonal contraceptive product must be from a Board of Pharmacy approved list, and provided in accordance with the state protocol. To be recognized as a furnisher of hormonal contraceptives, the pharmacist must successfully complete a minimum of one hour of a Board-approved continuing education program covering basics of furnishing hormonal contraceptive agents.
Pharmacists Furnishing Nicotine Replacement Products

Under CCR Section 1746.2, a pharmacist furnishing prescription-form nicotine replacement products must comply with a protocol approved by the California Board of Pharmacy and the Medical Board of California. When furnishing a nicotine replacement product, the pharmacist is required to develop and maintain a record of the patient’s response to certain key questions on their individual history and use of tobacco products, such as: (a) review of current use; (b) status of being or planning to be pregnant; and (c) general questions about the patient’s health, and in particular questions about cardiovascular diseases or disorders. In order to furnish such products, the pharmacist must follow the enumerated policies and procedures associated with prescription nicotine replacement products.

Since these products come in a variety of forms (gum, lozenges, patches, nasal sprays, and inhalers), the pharmacist’s judgment in making recommendations concerning nicotine replacement products is invaluable. Similar to other pharmacist patient care protocols, when a prescription nicotine replacement product is provided to the patient, the pharmacist must notify the patient’s primary care provider of the product furnished. If the patient does not have a primary care provider, the pharmacist shall provide the patient with a written record of the prescription drug provided, advise the patient to consult a health care provider, and make the information given to the patient also available to the health care provider.

The pharmacist is further required to complete a minimum of two years which focuses on smoking cessation therapy and nicotine replacement therapy.

Pharmacists Furnishing Travel Medications

The Board of Pharmacy has also proposed the addition of CCR Section 1746.5 to extend a pharmacist’s scope of practice to travel medications. The final proposed regulation text for CCR Section 1746.5 is currently pending in the Office of Administrative Law (OAL), and consistent with ordinary rulemaking procedures, once the text is approved by OAL, the regulation shall become effective on the first day of the following quarter, unless the board requests and is granted an earlier effective date by OAL. As proposed, will permit specially trained pharmacists to furnish travel medications to patients traveling outside the United States, and since the provision has not yet been finalized, the associated implementation regulation may have additional amendments or modifications prior to its ultimate adoption. Once CCR Section 1746.5 becomes operative, the law will require the pharmacist to:

(1) Complete requisite training, including:
   (a) An approved travel medicine training program, which must consist of at least 20 hours and cover each element of the International Society of Travel Medicine’s Body of Knowledge for the Practice of Travel Medicine;
   (b) The CDC Yellow Fever Vaccine Course;
   (c) A certificate course in basic life support;
   (d) A minimum of two hours of continuing education focused on travel medicine, which can be part of the pharmacist’s usually required 30 hours of continuing education every two years.

(2) Perform a good faith evaluation prior to furnishing travel medication, including evaluation of a patient’s travel history using destination-specific travel criteria. The travel history must include all the information necessary for a risk assessment during pretravel consultation, as identified in the CDC Yellow Book.

(3) Provide required notification to the patient’s primary care provider of any drugs and/or devices furnished to the patient within 30 days of the date of dispensing those drugs or devices. If the patient does not have a primary care provider or is unable to provide contact information for his or her primary care provider, the pharmacist shall provide the patient with a written record of the drugs/devices furnished and advise the patient to consult a physician of the patient’s choice.

(4) Maintain required documentation for each travel medication provided by the pharmacist, which includes a patient medication record maintained and securely stored in a physical or electronic manner such that the information is readily retrievable during the pharmacy’s normal operating hours. A pharmacist providing patients advice on travel medicine shall provide the patient with a progress note fully documenting the clinical assessment and travel medication plan. Proposed text for CCR 1746.4 provides that the pharmacist shall also provide the patient with a written document that reflects the clinical assessment and travel medication plan.

In summary, the only authority announced in SB 493, but which has yet to be implemented (at the time this article is written) pertains to the authority on travel medicines, for which final approval is pending in the Office of Administrative Law (OAL). According to the procedure, once the travel medicine regulation text is approved by OAL, the regulation “becomes effective on the first day of the following quarter, unless the board requests and is granted an earlier effective date by OAL.” Notwithstanding that, by the time this article appears in print, the various pharmacist authorities granted under SB 493 should be fully implemented. More detailed information discussing various SB authorities can be found at http://www.pharmacy.ca.gov/about/sb493.shtml.
What Does the Future Hold for Pharmacists as Patient Care Providers?

This discussion illustrates how laws encouraging pharmacists to become more engaged in direct patient care have evolved over the years. However, most recently, the landscape of health care delivery appears to be changing so rapidly that it seems almost naive to expect that our pharmacy profession will keep pace with it. That begs the question: What should education and training in a Doctor of Pharmacy (PharmD) program look like to keep up with the evolving health care landscape? Whether by dosage adjustments or initiating drug therapy, the pharmacy profession is certain to carve out new and evolving roles in new and evolving practice contexts, which the academy of pharmacy educators is already incorporating into the PharmD curriculum. Senator Hernandez’s SB 493 initiative has conferred extended significance to a pharmacist’s role in today’s world of proliferating medication use by patients. Moreover, SB 493 accomplished much more than simply recognizing pharmacists as health care providers. SB 493’s adoption into law in October 2013 provided both form and substance to what a pharmacist can do, and how pharmacists can play a vital role in providing patient care services.

As this article goes to press, all but one of the advanced practice authorities has been implemented. The proposed protocol under CCR Section 1746.4 for pharmacists to provide travel medicines is still pending review in the OAL; however, it remains likely to be approved and implemented very shortly. The pharmacy profession should look forward to these new direct patient care responsibilities serving as an impetus for further expansion of the scope of clinical pharmacy practice. The authors would like to believe that full implementation of SB 493’s provisions unlocks a passageway toward clinical pharmacy services either yet to be defined, and/or the adoption of pharmacy services that may currently be in a testing phase. The pharmacy profession will continue to make inroads to expand the scope and paradigm of pharmacy practice, as well as the multitude of contexts in which pharmacists serve in a clinical capacity, such as under physician-directed protocols in specialty clinics, managing asthma, hypertension, anticoagulation, oncology, psychiatric disorders, and diabetes therapies.

New doors of opportunity are certain to open for pharmacists striving toward clinical practice, monitoring, and improving patients’ health outcomes where their medical conditions are treated or controlled with drug therapy. Perhaps the even grander implication of SB 493 suggests that one day, physicians will diagnose and pharmacists will decide the specific drug therapy that a patient needs, and thereby pave the way for the pharmacist of the hopefully near future to be recognized and/or liberated as the drug prescriber rather than simply the drug furnisher linked to a particular prescriber-directed protocol. Of course, only time will tell…and … well, we shall see!

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