Using Real-World Evidence in Payer Negotiations
What's in Your Playbook?

Ariel Berger, MPH
Senior Research Scientist and Director, US Database Analytics, Real-World Evidence, Evidera

Cheryl Ball, BSFS
Vice President, General Manager, Market Access Consulting, Evidera

Ariel Berger

Cheryl Ball

Introduction

Rapid payer formulary acceptance with minimal restrictions can accelerate uptake, supporting successful product launch and commercial success. Similarly, maintaining or even expanding patient access to your product against competitors provides continued success for the product prior to loss of exclusivity. Regardless of your scenario, the generation and strategic use of real-world evidence (RWE) plays an important role in acquiring – and defending – optimal payer position, thereby enhancing return on investment.

However, not all RWE is created equal, and defining the strategy that can support a strong case for your product is dependent on a number of factors, including but not necessarily limited to the following: 1) where the compound is in terms of product lifecycle (e.g., early clinical, ready for launch, post-launch); 2) insight into the disease environment and relevant patient characteristics; 3) the competitive environment including the characteristics and performance of your competitors' products; and, 4) a strong position on how your product offers differentiated clinical, economic, and/or humanistic value. While RWE can provide value at all stages of the product lifecycle, in this article we provide some examples from our playbook that demonstrate how it can be used to align with payers on environment and value versus competitors at launch; defend payer positioning; and potentially even bolster and extend the value of on-market products.

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Readying for Launch: Establishing the Playing Field

Manufacturers need to prepare for negotiations with payers involving the value of a new product; formulary position, restrictions, and management; and, financial impact, discounts, rebates, or other contract elements. These negotiations are intense at launch, and the conversation is continued across the lifecycle as the funding environment changes, contracts are considered for renewal, or new data or new products are introduced that could impact market access.

In order to establish a baseline for constructive communication and negotiation, it is important that the manufacturer and payer develop a shared understanding and agreement on key elements of the playing field, such as (but not necessarily limited to): definition(s) of

the population(s) of interest, treatment(s) of interest, and outcome(s) of interest. Without a common understanding of, and agreement on, the current environment, manufacturer communication on product value may not be understood or appreciated. While this seems straightforward, there are a number of reasons why a payer's perception of the current environment may differ from that of the manufacturer, including differences in definitions and methods. Moreover, information shared with the payer will likely only resonate to the degree that it reflects their particular population. As a result, manufacturers may struggle to convey their product's potential to positively impact that baseline environment. Without clear, common, and accepted methods applied to the unique population covered by the payer, the limited time available for face-to-face discussions may be spent primarily on attempts to understand and resolve differences in methods or differences in the payer's population, rather than share information on the new product's value.

RWE provides a perfect opportunity for manufacturers to help payers appreciate the burden of disease in their "unique" population, and to understand how the manufacturer's product may benefit their patients, providers, and/or bottom line. One potential method by which this can be accomplished is by offering to serve as a research partner. Specifically, by proactively developing study protocols and/or statistical analysis plans that include a detailed description of the sample selection process, explicit definitions for all operational measures, and a means by which data should be output (e.g., table and figure shells), the manufacturer can provide an individual payer with the means to generate RWE that is specific to their population *and* focused on case definitions and operational measures relevant to the product. Once the playing field is established by these prespecified methods, subsequent conversations between the manufacturer and the payer can then focus on any and all of the following:

- The incidence/prevalence of the condition within the payer's specific population;
- The current burden of illness/magnitude of unmet need among these patients that highlights items of key relevance to the product's value proposition;
- Treatment patterns (including but not necessarily limited to adherence, persistency, discontinuation, and/or switching among particular products/classes);
- Safety of particular competitor products; and/or
- Comparative effectiveness (limited to instances where the product is already available).

By removing issues of methodology from the equation, the manufacturer can focus attention on what is of key interest – identification of the magnitude of a potential health issue and the extent by which it can be addressed by access to a newly launched product (or expanded access to an existing one).

Going on the Offensive/Playing Defense with RWE

Established competitors with an entrenched position and/or established financial incentives can create market stasis; other challenging issues for manufacturers include (but are by no means limited to) clinician attitudes stemming from confidence borne of hands-on experience, prevailing treatment guidelines that list competitors as preferred treatment options, and/or other disease-specific issues (e.g., antimicrobial stewardship). Without (and even sometimes with) price concessions, it can be difficult to overcome payer and/or clinician inertia and obtain market access that is minimally constrained.

Successful payer negotiations for a new product can be supported by identifying the economic and clinical limitations of current established products that could be offset by the new product's value proposition. Real-world evidence is a key means by which to identify and disseminate these limitations, as established products may perform different in clinical practice than they do in clinical trials for multiple reasons. Some of these reasons may in fact create risk for the established drug and aid in building the case for unmet needs the new product could address, including the following:

- The population studied in the trial is unlikely to perfectly mirror the population that ultimately takes the drug. Among other factors, patients may be older, sicker, or have more comorbidities, all of which may impact the outcomes achieved and even tolerability of the drug in practice, creating opportunities for improvement.
- Similarly, the established product may demonstrate weaker performance in a specific population (e.g., with a certain biomarker, comorbidities, disease status) where a novel product performs particularly well.
- The established product may result in levels of utilization and cost of healthcare resources that are greater than expected.
- Safety monitoring in trials is unlikely to uncover all adverse events that occur, and may not fully reflect associated resource utilization/cost to the payer.
- As patients are typically followed less closely in real life than during a clinical trial, they may be less adherent to medications, resulting in suboptimal dosing. With potentially less-frequent exposure to

healthcare practitioners, patients may engage in less optimal behaviors, influencing outcomes negatively. While a novel product may face similar risks, different routes of administration and/or dosing regimens (including long- versus short-acting agents) may inherently reduce the risk of suboptimal dosing.

Alternatively, a clinical trial may be powered for non-inferiority, which is sufficient grounds for regulatory approval but does not provide payers with clear guidance as to which patients merit access to the newly approved product (versus "non-inferior", and potentially less expensive, comparators). The latter issue is especially problematic if the manufacturer did not include economic endpoints in their trial(s) that may provide differentiation between products.

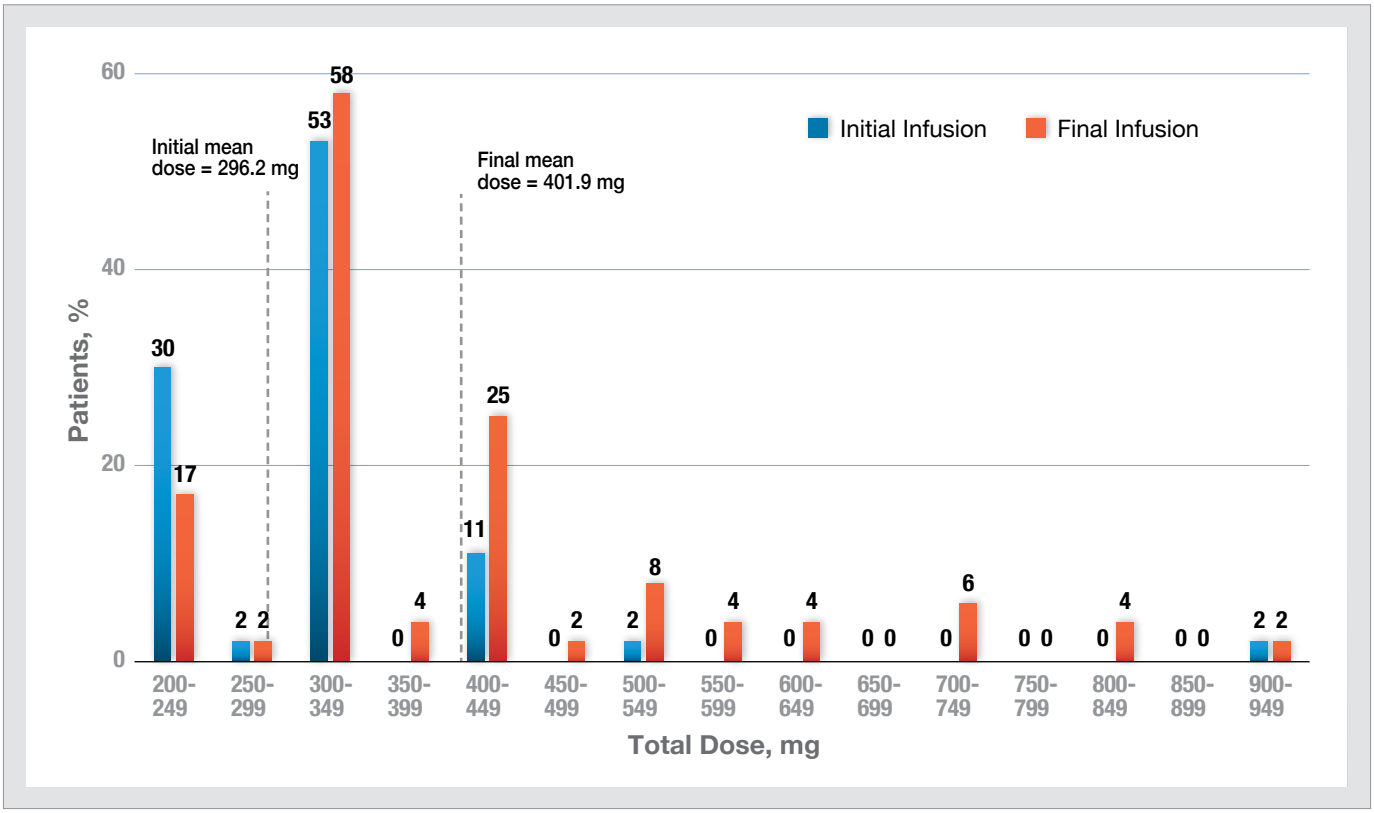
Once your product is in the established position, planning ahead can help prepare you to defend its position from new entrants. Naturally, some of the same vulnerabilities you identified in competitors at launch could apply to your product once marketed and used. Strategic use of RWE can potentially support maintaining or even improving your access over time, and in the face of competition.

Some of the potential opportunities to defend or expand position for an established product include:

- Proven impact on "hard" outcomes such as reduced event rates (e.g., mortality, costly events such as surgeries or hospitalizations) versus surrogates measured in trials. These can be more powerful if there are key differences to novel products, such as mechanism, that would call into doubt whether similar impact on surrogates of the novel drug would have similar outcomes.
- Evidence of value in high-risk or difficult-to-treat populations that might not have been studied in trials, or where there might not have been significant data
- Evidence of reduced use and/or cost of healthcare resources
- Evidence of long-term safety
- Evidence of strong adherence that in turn is associated with positive outcomes

Some examples of the use of RWE for these purposes from our own personal experiences are provided below. One such example where actual drug utilization significantly exceeded utilization expected based on package inserts (and by extension, trial data), creating higher drug costs but also uncertainty on safety and outcomes, is a previous examination of patterns of use of infliximab (Remicade®) among patients with rheumatoid

Figure 1. Frequency Distribution of Initial and Final Dose of Infliximab



arthritis (RA) identified in a large U.S. healthcare claims database. In this study, a total of 53 patients with RA were identified who initiated therapy with infliximab between January 1, 2000, and September 30, 2001; the date of initiation of infliximab was designated the index date, and attention was focused on patients who received infliximab for at least 1 year subsequent.[1] The authors contrasted "real-world" use of infliximab over the 1-year period following the index date – in terms of the number of infusions of infliximab received and corresponding doses thereof – with recommendations set forth in the package insert. Over the 1-year study period, 28% of patients received >8 infusions (based on package labeling current at the time the study was undertaken, patients with an adequate response to infliximab should receive 8 infusions of such therapy over 1 year). The mean dose of infliximab increased from 296.2 mg during the initial infusion to 401.9 mg at the final infusion *(Figure 1)*. While patient weight was unavailable in the data, calculations done by the authors based on the average weight of persons with RA in the U.S. suggested that the initial dose of infliximab was closer to 4 mg/kg than the recommended starting dose of 3 mg/kg. Dose increases were common – one-half and one-third of patients experienced dose increases between their initial and final infusions of ≥30% and ≥50%, respectively. Taken collectively, this study indicated that in clinical practice, physicians initiate infliximab at a dose higher than suggested by the package insert and frequently increase dose and/or number of administrations over the course of the first year of therapy, despite the corresponding increase in risk of adverse events. Accordingly, findings from this study could potentially be used to highlight potential concerns associated with use of infliximab for RA, based exclusively on RWE.

Spotlight on Relevant Subgroups

Another set of examples come from examinations of use of various medications among elderly patients (i.e., age ≥65 years) with painful neuropathic disorders (PNDs) and generalized anxiety disorder (GAD), respectively; the former was assessed in a U.S. database and the latter in a German database. Causes of PNDs are varied, and include diabetes, infection with herpes zoster, acquired immune deficiency syndrome (AIDS), and nerve compression and entrapment syndromes. Their treatment is difficult, as the effectiveness of opioids and other "traditional" analgesics is limited; typically "adjuvant" analgesics such as antiepileptics and antidepressants are required. GAD, which is a chronic disorder characterized by persistent worry or anxiety more days than not for ≥6 months, is the most common anxiety disorder among patients presenting to primary care physicians.[2,3] Several different medications are used to treat GAD, including benzodiazepines (which have long been considered the mainstay of therapy), buspirone, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and venlafaxine.

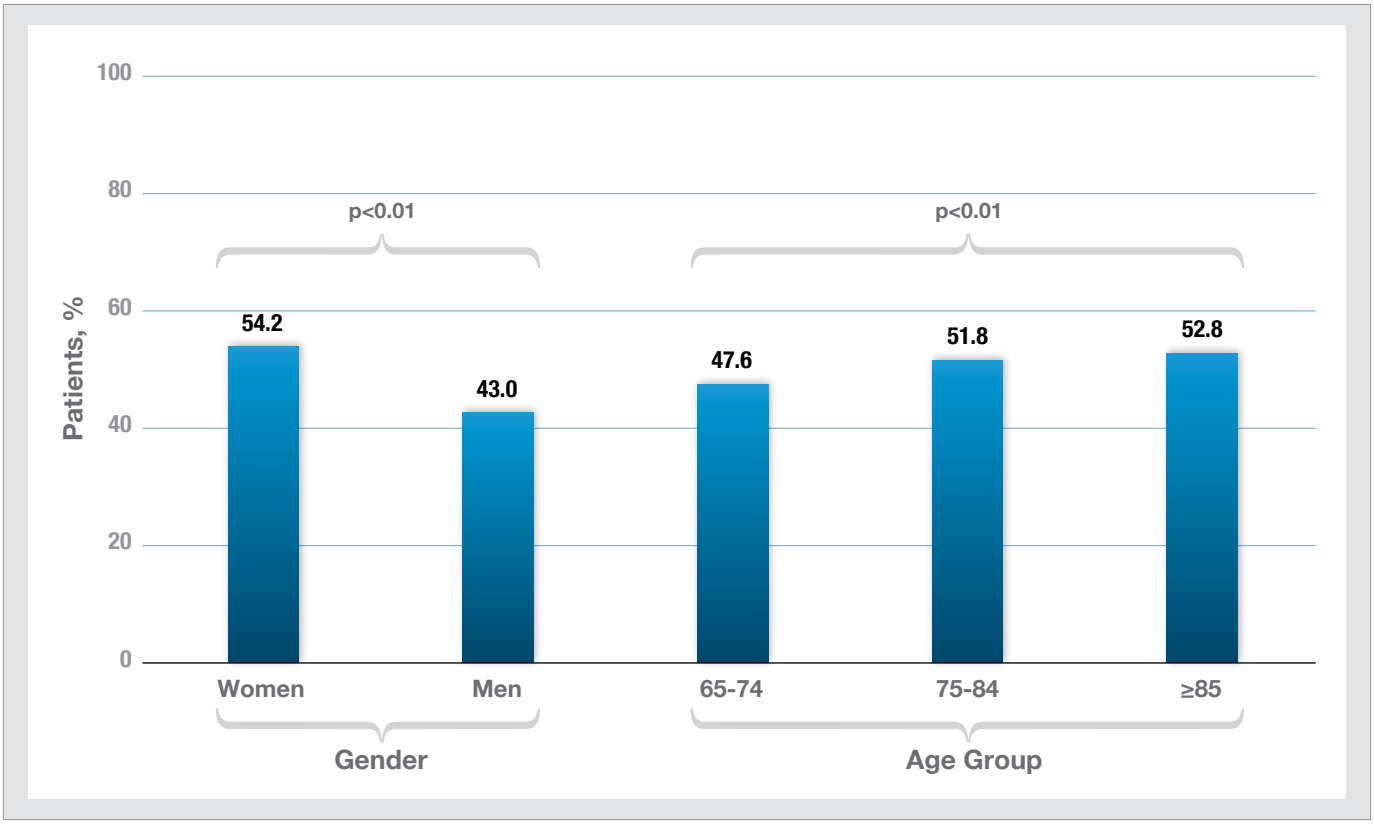
As patients age, their ability to metabolize medications decreases. In 1997, a panel convened by Mark Beers identified a number of medications that were deemed "potentially inappropriate" for use in elderly patients irrespective of indication or place of residence (e.g., nursing home versus community), and that were limited to agents with greater potential for harm than benefit.[4,5] These criteria, which were subsequently updated by Zhan,

Table 1. Potentially Inappropriate Medications Used to Treat PNDs and/or GAD

Medication	Used to Treat PNDs	Used to Treat GAD
Indomethacin	Yes	No
Opioids	No	No
Propoxyphene and propoxyphene combination products	Yes	No
Pentazocine	Yes	No
Meperidine	Yes	No
Skeletal muscle relaxants		
Methocarbamol	Yes	No
Carisoprodol	Yes	No
Chlorzoxazone	Yes	No
Metaxalone	Yes	No
Cyclobenzaprine	Yes	No
Tertiary tricyclic antidepressants		
Amitriptyline	Yes	Yes
Chlordiazepoxide-amitriptyline	Yes	No
Perphenazine-amitriptyline	Yes	No
Doxepin	Yes	Yes
Benzodiazepines*	Yes	Yes
Meprobamate	Yes	No
Hydroxyzine	Yes	Yes
Promethazine	Yes	No

*Lorazepam, oxazepam, alprazolam, flurazapam, temazepam, zolpidem, chlordiazepoxide, chlordiazepoxide-amitriptyline, diazepam, bromazepam, lormetazepam, nitrazepam, oxazepam, tetrazepam, triazolam, chlorazepate, flunitrazepam, flurazepam, halazepam, medazepam, nordazepam, prezepam

Figure 2. Use of Potentially Inappropriate Medications among Elderly Patients in the US with PNDs



et al. to possibly allow for some instances where these medications may be appropriate (i.e., drugs that should always be avoided, drugs that are rarely appropriate, drugs that are appropriate for some indications)[6] include a number of different medications commonly used to treat pain and/or GAD *(Table 1)*. While the criteria are not without their limitations, they have often been used to assess potential safety risks associated with medication prescribing among the elderly.[6-14]

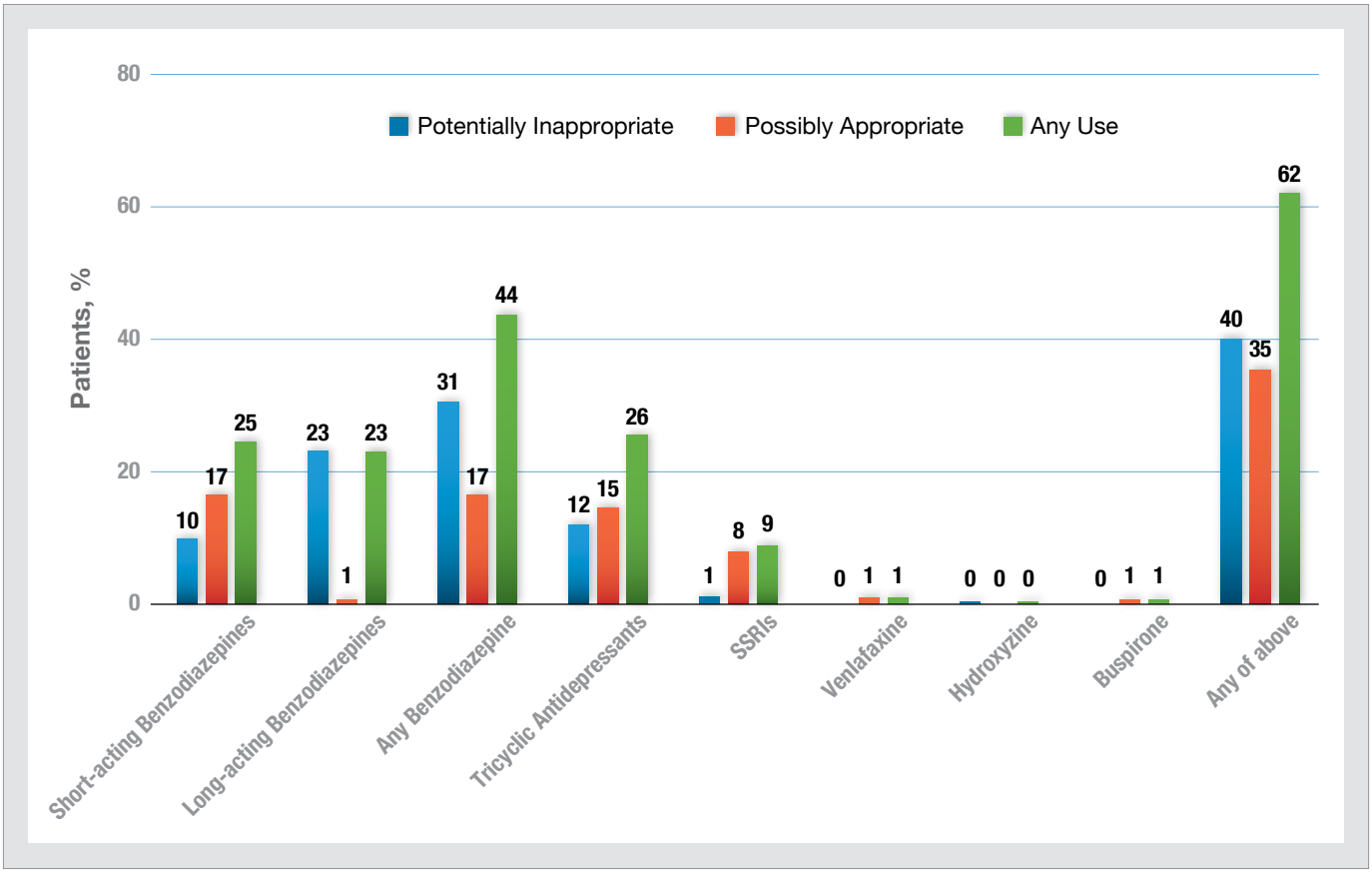
Using a large U.S. healthcare claims database, a total of 22,668 elderly patients with PNDs were identified during 2000; nearly one-half (49.6%) of patients received at least one potentially inappropriate pain-related medication during the year.[15] Women were more likely than men to receive such medications, and use increased with age (p<0.01 for all comparisons) *(Figure 2)*.

"Taken collectively, results of these studies suggest that in multiple markets, the prescribing of potentially inappropriate medications to elderly patients with chronic, often debilitating, conditions is a relatively common phenomenon."

Using a German database with information from encounters with general practitioners (GP), a total of 975 elderly patients with GAD were identified between October 1, 2003, and September 30, 2004; 40% received at least one potentially inappropriate medication during the year, including long-acting benzodiazepines (23%), short-acting benzodiazepines at relatively high doses (10%), and tricyclic antidepressants (12%).[16] Unlike the PND study described above, the authors classified receipt of medications as potentially inappropriate or possibly appropriate, based on the aforementioned updated criteria from Zhan, et al. and information on daily dosage contained within the database *(Figure 3)*.

Taken collectively, results of these studies suggest that in multiple markets, the prescribing of potentially inappropriate medications to elderly patients with chronic, often debilitating, conditions is a relatively common phenomenon. While the precise reason(s) underlying observed prescribing patterns are not discernable from the data sources used, it is likely that contributing factors include clinician familiarity with the products (benzodiazepines and propoxyphene were first approved decades previously), acquisition cost (many of the products on Beers' [and subsequent authors'] lists

Figure 3. Use of Potentially Inappropriate Medications among Elderly Patients with GAD in Germany



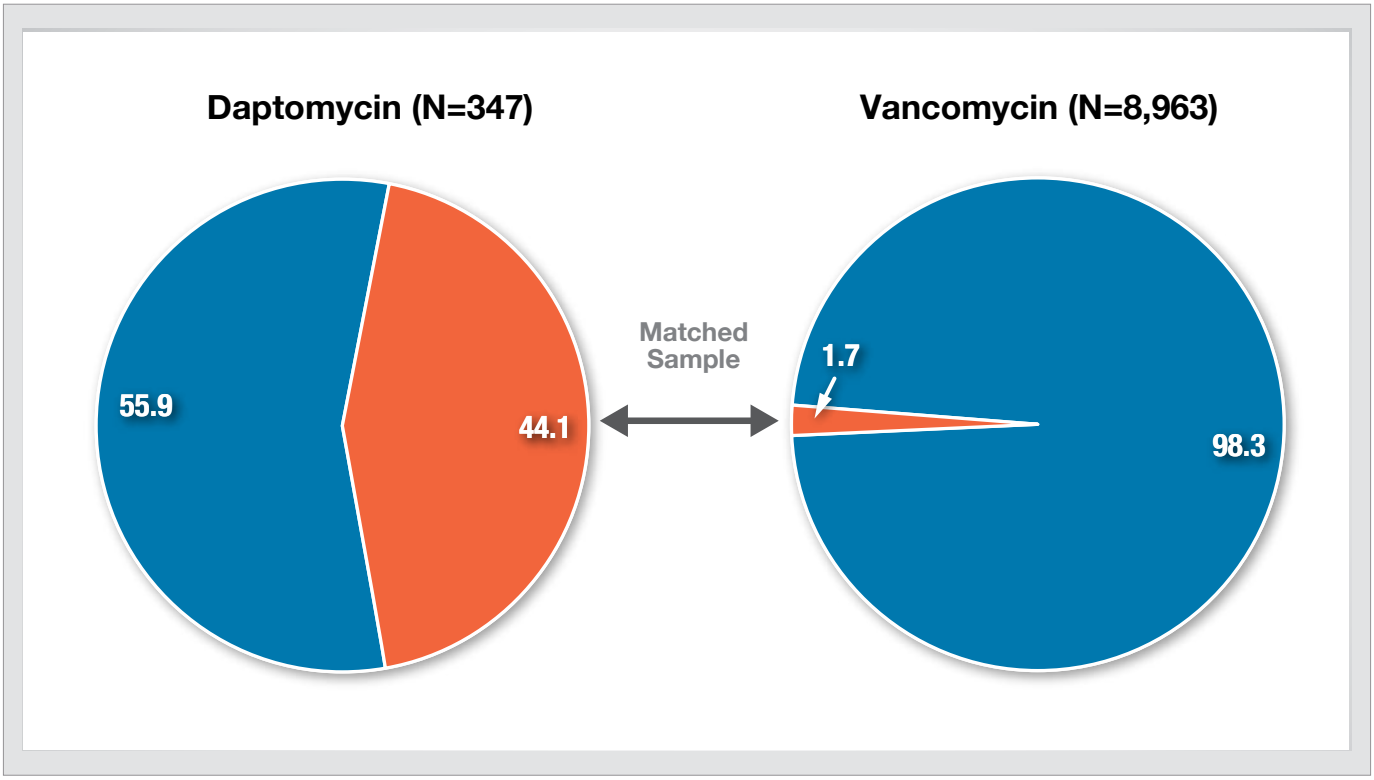
are available as generic preparations), and published treatment guidelines that do not differentiate suggested treatments by patient age (benzodiazepines, buspirone, TCAs, and SSRIs are all recommended for GAD,[17-19] with no distinction made for age). While clinical and economic consequences associated with prescribing of these potentially inappropriate medications were not assessed in either study, it stands to reason that this RWE, coupled with education on alternative medications with demonstrated efficacy in PND or GAD and relatively favorable safety profiles among the elderly may give providers and/or payers reason to entertain arguments in favor of relatively safer alternatives in this "at-risk" population.

Elevating the Game

While RWE is used to inform payer negotiations and help support market access decision making, a limiting factor can be access to appropriate data. After all, your evidence is only as good as the data upon which it is based. While many questions – especially those in support of products currently on the market – can be addressed using existing data sources, such as healthcare claims, electronic medical records (EMR), chart reviews, and/or encounter databases (hospital- or physician-based), there are times when such sources cannot be leveraged. Reasons that preclude use of these sources are somewhat varied, but tend to focus on one of two issues – the source does not contain the information necessary to address the question (e.g., traditional claims data lack patient-reported outcomes, reason[s] for prescribing, or detailed clinical measures) or the concern that comparisons of interest suffer from potential confounding data that cannot be addressed from available information. As the former is fairly self-explanatory, we will focus our final example on the latter.

Complicated skin and skin-structure infections (cSSSI), which are commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA), typically require admission to hospital and use of parenteral antibiotic therapy. While vancomycin is considered the "workhorse" in this area for a number of reasons (e.g., physician familiarity [it was approved in the 1950s], low acquisition price, place in treatment guidelines, concerns around antimicrobial stewardship), it may not always be the optimal choice. Newer agents (e.g., linezolid, tedizolid, daptomycin, ceftaroline, dalbavancin, oritivancin) may offer additional benefit (e.g., reduced dosing schedules potentially reducing or even precluding admission to hospital, easier parenteral-to-oral conversion thereby optimizing adherence post-discharge, reduction in risk of

Figure 4. Distribution of Matched and Unmatched Patients



development of vancomycin-resistant S. aureus [VRSA]) albeit at higher acquisition prices). Further complicating the issue is that Phase III clinical trials of antimicrobials are typically powered for non-inferiority (as opposed to superiority), which limits the usefulness of data generated during the clinical development program in supporting arguments in favor of expanding market access for the newer products.

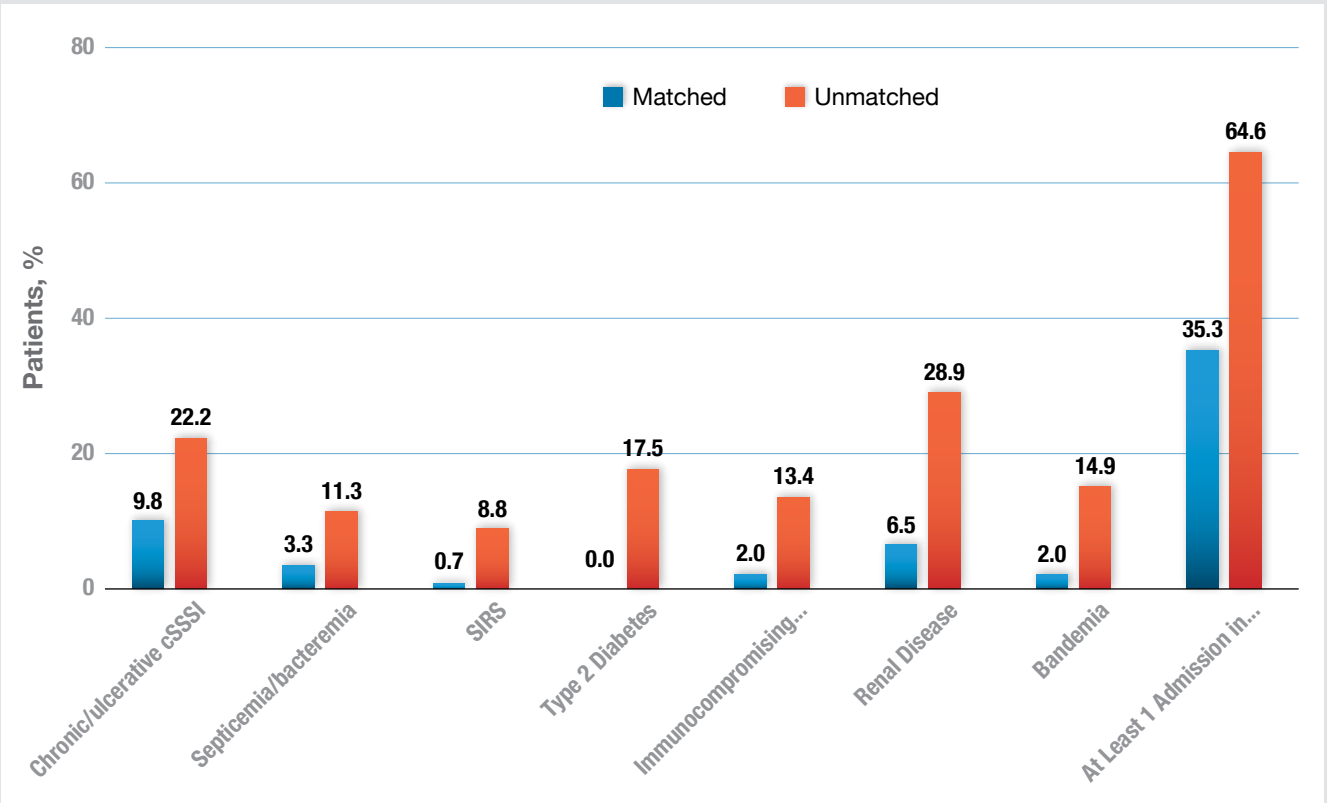
Could RWE based on existing data be used to support arguments in favor of use of newer products? In a prior study that sought to compare selected outcomes and costs among cSSSI patients treated with vancomycin versus daptomycin,[20] a total of 9,310 admissions to hospitals involving use of vancomycin or daptomycin as initial antibiotic therapy for cSSSI between January 1, 2007, and June 30, 2010, were identified in a large U.S. hospital database; 8,963 patients (96% of the study sample) received initial therapy with vancomycin. Interestingly, four hospitals contributed 54% of daptomycin cases, but only 17% of vancomycin cases; the hospital with the largest proportion of daptomycin cases (28% of all such patients) contributed only 4% of vancomycin cases. As the demographic and clinical characteristics of daptomycin patients differed from those of vancomycin patients, the former were matched to the latter on the basis of propensity scores. However, while propensity-score matching led to clinical equipoise between the groups, it also resulted in the exclusion of more than one-half of daptomycin patients and nearly all (98%) vancomycin patients for whom matching could not be done *(Figure 4)*. Paradoxically, in order to maximize internal validity by controlling for observed selection bias that would confound comparisons of the two agents, most "real-world" patients treated with either antimicrobial were *excluded* from the study, thereby threatening external validity.

"Unlike clinical trials ... the purpose of a pragmatic trial is to establish effectiveness of interventions in real-world settings."

Patients for whom matching was successful also differed substantially from their unmatched counterparts – specifically, matched daptomycin patients were younger (mean age = 52 years vs. 57 years for unmatched patients); they also had different types of cSSSI, were less likely to have clinical markers for severe infection, and were less likely to have comorbidities ($p<0.01$ for all comparisons) *(Figure 5)*. Similarly, matched vancomycin patients tended to be relatively sicker than their unmatched counterparts (data not shown).

The generalizability of the resulting sample to all real-world cSSSI patients treated with daptomycin versus

Figure 5. Characteristics of Matched and Unmatched Daptomycin Patients*



*p<0.01 for all comparisons

vancomycin was unknown and likely low due to the relatively small number of patients for whom matching could be done and the fact that analyses would be limited to the "worst" cases treated with vancomycin versus the "best" cases treated with daptomycin (i.e., use of daptomycin as first-line therapy in the "real world" appeared for the most part to be focused on different patients than those for whom vancomycin was used). Moreover, despite matching, substantial concerns remained around selection bias (i.e., residual confounding) at the physician and/or institution level that could not be addressed with information available in the database. In instances like this – and those for which existing data do not contain the information necessary to conduct the appropriate comparisons – alternative study designs such as pragmatic trials are required. Unlike clinical trials, which focus on ascertaining the efficacy of an intervention in well-defined settings that are designed to control for all known biases/sources of confounding, the purpose of a pragmatic trial is to establish effectiveness of interventions in real-world settings. Accordingly, pragmatic trials tend to embrace an "all comers" approach, and use as comparators other "active" interventions in order to address the policy question as to whether current thinking on appropriate treatments should be changed. While not without their own challenges, in instances where existing data are unavailable/found insufficient to address your needs, these designs allow for the analyses required to generate the RWE necessary to influence payers to gain, retain, and/or expand market access.

Conclusion

Across the product lifecycle, a delicate and never-ending game is played between manufacturers and payers. While both sides share a common goal of improved patient health, reduced physician burden, and decreasing burden of illness, they tend to differ on their approach. Developing a playbook that sets forth your approach to the generation of RWE that can support your product's value and differentiation can enhance and accelerate payer negotiation and improve total lifecycle revenue. Appropriate and timely use of RWE has the potential to help you ground payer discussions in the specific dynamics of their population of interest (within a specific country or health plan), aligned with treatment patterns and resource use that occur within their purview. For manufacturers, the result of these conversations is to move the game to their playing field, potentially creating greater impetus to value products – and by extension – winning the game by gaining and ultimately expanding provider and patient access to their products. ■

For more information, please contact Ariel.Berger@evidera.com or Cheryl.Ball@evidera.com.

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