Criteria for the Use of Tramadol in Adult Patients: Medication-Use Evaluation Guidelines

Joyce A. Generali and Alan H. Heaton

OBJECTIVE: To develop a practical medication-use evaluation (MUE) tool flexible enough to be used in a variety of practice settings

SETTING: Institutional health care systems or managed care organizations, although the format may be adapted for use by consultant pharmacists.

DESIGN: This MUE has been designed for use as part of a comprehensive outcome monitoring program. It focuses on a particular agent (tramadol hydrochloride) that has significant cost and usage implications.

MAIN OUTCOME MEASURES: Appropriate patient populations and desired therapeutic outcomes can be identified with the use of this MUE. Customized interventions that are appropriate to each organization may

be built into the framework supplied by this article.

RESULTS: This MUE can provide a framework for institutional health care systems and MCOs to use in developing a comprehensive monitoring program for tramadol hydrochloride and an oral analgesic.

CONCLUSION: Effective high-quality pharmaceutical care incorporates the use of assessment methods that monitor patient outcomes and medication-use processes. Patient outcomes may be improved through proper application of the MUE process.

KEYWORDS: Medication use evaluation, Patient outcomes, Tramadol HCl

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Ten years ago, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) began mandating an evaluation of patient outcomes as part of the measurement of continuous improvement in quality of patient care. Ensuring appropriate use of medications optimizes patient outcomes, improves the safety and efficacy of drug therapy, and minimizes the expense of health care. Pharmacists in all areas of practice are uniquely qualified to conduct drug use evaluations (DUEs).¹ Although traditionally applied in the hospital setting, DUE today is a quality-assessment tool used by managed care and long-term care organizations as well.

Recently, the focus of drug-use evaluation has evolved from a retrospective review of antibiotics or other high-cost pharmaceuticals into a comprehensive prospective evaluation of patient outcomes—a type of drug therapy assessment that is better defined by the term “medication-use evaluation” (MUE).² As the drive to maintain high quality health care continues, providing effective pharmaceutical care requires the use of quality assessment instruments that incorporate the monitoring of both patient outcome and medication-use patterns.

EVOLUTION OF THE MEDICATION-USE EVALUATION PROCESS

Evaluating drug therapy for appropriate use and outcomes monitoring provides the cornerstone of effective pharmacotherapy. Historically, drug-use evaluation has served as the traditional tool to evaluate whether medications were prescribed, used, and monitored in a safe and rational manner.³

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JCAHO has deemed evaluation of drug therapy to be a recognized standard in the accreditation process. Earlier programs focused narrowly on the quantitative aspects and patterns of drug use, were retrospective in nature, were typically centered on antibiotics, and were often isolated evaluations with little participation outside of pharmacy circles.

During the past decade, the scope of MUE has broadened to evaluate the use of a wide range of drug products in various patient populations and health care settings. Medication use evaluation now emphasizes improving outcome and patient quality of life. The MUE process may be used for a single agent or a therapeutic class of drugs, a specific process related to use of medications, a defined disease state, or a selected outcome.² Multidisciplinary involvement of physicians, nurses, and other health care providers is integral to the current expanded process as described in recent American Society of Health-System Pharmacists (ASHP) and JCAHO guidelines.^{2,4}

PATIENT OUTCOMES

The importance of measuring patient outcomes to assess the quality of health care provided by an organization has led to the development of several health care management tools, including critical pathways and clinical care plans. Critical pathways are detailed plans of care for a specific diagnosis, disease, or procedure in which the appropriate use and timing of therapeutic interventions are defined to optimize resource management, minimize cost, and improve patient outcome.⁵ Reports have documented the effectiveness of critical pathways in decreasing length of hospitalization, reducing overall costs of care, and minimizing complications.⁶ Similarly, clinical care plans incorporate disease state, provision of care, and drug therapy.

Appropriate medication use remains an important component in producing positive patient outcomes. Patient-focused MUE will remain an essential part of the critical care pathway or clinical care plan process.

THE MEDICATION-USE EVALUATION PROCESS

Despite several evolutionary changes in the methods for evaluating medications, the general purpose remains the same: to provide an objective assessment of drugs against established criteria. Medication-use evaluations are designed to define optimal treatments or conditions, identify actual or potential problems related to medication use, and resolve or prevent any identified problems that may interfere with achieving optimal therapeutic outcomes. Patient-related data are usually collected and assessed to verify the rational use of medications in a continuous monitoring system. Although early programs were often retrospective in nature, the greatest potential for impact on patient care lies in applying the MUE process prospectively or concurrently. Overall, the goals of an MUE are to optimize drug therapy, to improve patient safety, and to minimize needless expenditures.⁷

Joint Commission Requirements

The foundation of an MUE is the objective assessment of a selected drug against established criteria composed of clearly defined indicators. The JCAHO has identified five major components related to medication use, including processes involving prescribing, dispensing, administration, monitoring, and systems/management control. The medical staff standards set forth by the JCAHO state that MUEs should incorporate at least two of these areas.⁴

Selection of Criteria and Indicators

When selecting medications for MUE monitoring, consideration should be given to agents used in high volume, in special populations, in high-risk disease states, or in patients experiencing a deterioration in quality of life during therapy.⁸ Other situations, such as the occurrence of adverse events or frequent treatment failures, may be used to prompt the start of the MUE process. Published criteria may be adapted for MUE within an organization. The use of published criteria is advantageous because they are ready to use, are well referenced, and are written by experts.⁹ Original criteria developed within a health care organization usually include input from pharmacy, nursing, and medical staffs. In addition, these criteria are usually reviewed by experts in the therapeutic field and approved by a pharmacy and therapeutics committee.

Criteria and indicators, as described by the JCAHO, are assessment tools used to monitor and evaluate the quality of governance, management, clinical, and support functions that affect patient outcome. Medication-use indicators may have several functions, such as describing a sentinel or rate-based event (e.g., undesirable outcome or serious adverse event) or a desirable process or outcome. Chosen indicators should be important to the quality of care provided by the health care organization, as well as being measurable, objective, sensitive, and specific. Sources for the information used in criteria and indicator development usually include clinical information obtained from a review of published literature, product information, and practice guidelines, when available.

APPLICATION OF THE MEDICATION-USE EVALUATION MODEL TO TRAMADOL HCL

Tramadol hydrochloride (HCl), an oral analgesic introduced in the United States in 1995, is an appropriate drug for MUE monitoring.¹⁰ The brand name of tramadol HCl tablets is Ultram, from Ortho-McNeil Pharmaceuticals. It has broad applications for use as an analgesic in moderate to moderately severe pain, is prescribed across many medical disciplines, and may be used in diverse adult patient populations (e.g., healthy young adults or older adults with chronic diseases). As a centrally acting analgesic with opioid and nonopioid mechanisms of action, tramadol HCl provides a therapeutic alternative for patients who are at risk of developing gastrointestinal bleeding

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Table 1. Medication Use Evaluation for Tramadol in Adults

Element	Standard 100% 0%		Exception or Critical Preventive/Response	Information Sources
Justification for use				
Moderate to moderately severe noninflammatory pain OR	X		None	1, 2, 3
Chronic joint pain AND	X		None	1, 2, 3
Present pain regimens ineffective OR	X		None	1, 2, 3, 4
Patient not a candidate for NSAIDs (hypertension, history of GI bleeding, COPD, elderly)	X		None	1, 2, 4, 5
Critical (process) indicators				
Tramadol is not used in patients:				
With history of hypersensitivity to tramadol, codeine, or other opioids	X		None	1
Younger than 16 years of age	X		None	1, 2
Who are pregnant or lactating	X		Use only with acceptable risk ratio	1, 2, 5
Who are acutely intoxicated by opioids, alcohol, hypnotics, centrally acting analgesics, or psychotropic drugs	X		None	1, 2, 4, 5
With past or present history of opioid or other drug dependency	X		None	1, 2, 3, 4
Who have history of, increased risk for, or are taking drugs that increase risk of seizures or lower seizure threshold (e.g., neuroleptics, MAOIs, opioids, TCAs, SSRIs or anorectics), or have a head injury or increased intracranial pressure	X		Use only with acceptable risk ratio Consider altered mental status as possible ADR	1, 2, 3
Appropriate adult dose of tramadol: 50–100 mg/ 4–6 hours PRN	X		Renal or liver dysfunction, or concurrent carbamazepine therapy	2, 3, 5, 6
Maximum daily dose for ages 16–75: ≤400mg daily				
Maximum daily dose for ages >75: ≤300mg daily				
Dose adjusted for renal dysfunction ▲ Clcr: if <30 mL/min, 50–100 mg/12 hrs maximum daily dose ≤200 mg ▲ Hemodialysis: 50–100 mg/12 hrs on day of dialysis	X		None	3, 5, 6
Dose adjusted for liver dysfunction: 50 mg/12 hrs	X		None	3, 5, 6
Dose adjusted with concurrent drug therapy: ▲ with carbamazepine ≤800mg/d (may require twice recommended tramadol dose) ▲ With CNS depressants (opioids, phenothiazines, sedative-hypnotics, tranquilizers, anesthetics)	X		None	2,3,6
			Monitor for additive CNS side effects; stop or reduce dosage	
Appropriate treatment duration based on acute or chronic pain	X		Monitor for efficacy	2, 6
If renal impairment suspected or known, obtain laboratory assessment before starting therapy: baseline Clcr available	X		Adjust dose accordingly	2, 4, 5
Complications—In all cases: identify other causes (drug, nondrug); provide symptomatic and supportive care; use alternative analgesic as needed				
Anaphylaxis: difficulty breathing, hypotension, cardiac arrest		X	Discontinue tramadol	2, 3, 4, 6
CNS: seizures, dizziness, headache, nervousness, tremor, sleep disorders, anxiety, abnormal gait, paresthesia, confusion, cognitive dysfunction, coordination disturbance, somnolence, CNS stimulation (emotional lability, agitation, spasticity, hallucinations)		X	Treat mild reaction symptomatically; stop tramadol with severe reaction	2, 3, 4, 6
GI: diarrhea, nausea, vomiting, constipation, flatulence, dry mouth, anorexia, abdominal pain, dyspepsia		X	Treat mild reaction symptomatically; stop tramadol with severe reaction	2, 3, 4, 6
Cardiovascular: vasodilation, orthostatic hypotension, tachycardia, syncope		X	Discontinue tramadol	2, 3, 4, 6
Skin: pruritus, rash, vesicles, diaphoresis		X	Treat mild reaction symptomatically	2, 3, 4, 6

Table 1. Medication Use Evaluation for Tramadol in Adults (continued)

Element	Standard 100% 0%	Exception or Critical Preventive/Response	Information Sources
Complications—In all cases: identify other causes (drug, nondrug); provide symptomatic and supportive care; use alternative analgesic as needed			
Body as whole: asthenia, malaise	X	Discontinue tramadol	2, 3, 4, 6
Respiratory: dyspnea	X	Discontinue tramadol	2, 3, 4, 6
Musculoskeletal: hypertonia	X	Treat mild reaction symptomatically; stop tramadol with severe reaction	2, 3, 4, 6
Renal: urinary retention, dysuria, urinary frequency, elevated Scr	X	Recheck abnormal values until reaching baseline or desired levels; adjust dose or stop tramadol	2, 3, 4, 5, 6
Genital: menopausal symptoms	X	Treat mild reaction symptomatically; stop tramadol with severe reaction	2, 3, 4, 6
Ocular: visual disturbances	X	Discontinue tramadol	2, 3, 4, 6
Clinical Outcomes			
Improved pain relief, clinical signs/ symptoms	X	No sign of initial pain/Monitor for breakthrough pain; consider additional or alternate analgesic therapy/Patient discharged before therapy complete Patient died	2, 3, 4

Information Sources: 1=H&P; 2=progress notes; 3=physician orders; 4=nursing notes; 5=laboratory reports; 6=medication administration record. In managed care organizations, other sources include enrollment, pharmacy claims, and ICD-9 codes.

ADR=adverse drug reaction; Clcr=creatinine clearance; CNS=central nervous system; COPD=chronic obstructive pulmonary disease; GI=gastrointestinal; H&P=history and physical; MAOIs=monoamine oxidase inhibitors; MAR=medication administration record; NSAIDs=nonsteroidal antiinflammatory drugs; PRN=as needed; Scr=serum creatinine; SSRIs=selective serotonin reuptake inhibitors.

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associated with nonsteroidal antiinflammatory drug (NSAID) use.^{11,12} Additionally, it may be useful for individuals who cannot tolerate other centrally acting analgesics or prolonged NSAID therapy.¹³ In chronic pain conditions, the use of tramadol HCl as monotherapy or adjunctive therapy may be an effective alternative to traditional centrally acting analgesics.¹⁴⁻¹⁶ Proper dosing regimens and appropriate patient selection for tramadol HCl use are important because recent changes in product labeling have clarified the population at risk for dependency and seizures; anaphylactoid reactions also have been described in certain populations.¹⁷

This evaluation was developed to assess the role of tramadol HCl in the management of pain in adult patients (see Table 1) and follows the format established by the ASHP.^{2,18} The criteria and indicators were based on information derived from the product information and a comprehensive review of the published literature.^{10,15,19-26} Information not included in the presented MUE (i.e., acquisition cost or cost of treating adverse effects) may be helpful in determining the economic impact and safety aspects of tramadol HCl for managed care and institutional formularies.

TRAMADOL HCL: THERAPEUTIC IMPLICATIONS FOR MEDICATION-USE EVALUATION

Identifying specific internal analgesic usage patterns (adjunctive versus monotherapy) and analgesic adverse-event occurrence rates by medical specialty may be meaningful in establishing a role for tramadol HCl use in certain patient populations. MUE criteria may be valuable in assessing an agent prior to its inclusion in a formulary by providing a description of how a drug is used in a care setting and identifying benefits, problems, or educational issues relevant to use of the medication. Once identified, this information can be used to create recommendations for use. In the case of tramadol HCl, identifying the areas in which it is prescribed (e.g., ambulatory clinics or inpatient situations) and the indications for which it is being used (e.g., musculoskeletal pain) can assist in the development of therapeutic guidelines for appropriate use.

Tramadol HCl Dosing

In the Critical Process Indicator section, the appropriate adult dose for tramadol HCl is listed as 50–100mg every four to six hours as needed.²⁷ Maximum daily doses are less than or equal to 300 mg in the elderly (>75 years) and less than or equal to 400 mg for adults aged 16–75 years. Because some patients may experience adverse effects upon initiation of tramadol HCl therapy, compliance may be enhanced through the

use of a dose-titration regimen as follows:

- ▲ Day 1, 25 mg (1/2 tablet) every four hours while awake
- ▲ Day 2, 50 mg every eight hours with 25 mg used for breakthrough pain as needed within four hours of a scheduled dose
- ▲ Day 3, 50 mg every six hours while awake and 25 mg as needed within three hours of a scheduled dose for breakthrough pain.²⁸

Once the acute painful episode has stabilized, dosage adjustments based on individual need have been successful in achieving the lowest possible patient-specific dose.

Adverse Drug Reaction Monitoring

In the hospital and managed care setting, identifying adverse reactions associated with analgesic regimens may be helpful in defining the place of tramadol HCl in organizational critical pathways. Adverse reactions can be tracked via established internal adverse-drug reaction reporting systems, internal databases, and reports generated from medical records coding for diagnosis (ICD-9 CM).²⁹ A subset of diagnosis codes, E-codes, captures the occurrence of adverse events. The E-code specific to analgesics is E935, with subsets for opiates and related narcotics (E935.2), salicylates (E935.3), aromatic analgesics (E935.4), and antirheumatic drugs (NSAIDs) (E935.6). This MUE captures adverse medication event information in the section entitled "Complications Element."

MEDICATION-USE EVALUATION: THE MANAGED CARE PERSPECTIVE

Application of the MUE process in the outpatient environment typical of a managed care organization (MCO) presents some special challenges. Sources of information used during the MUE process are often claims databases. However, the availability and accuracy of ICD-9 coding for diagnosis historically have been less than completely reliable.³⁰ Clinical data, readily found in the patient's chart in an institution, are usually not retrievable without extraordinary mechanisms in the managed care setting. Fortunately, pharmacy claims data are uniform and "clean." Consequently, special rules or field markers can be created to highlight areas of concern for an MUE. For example, discontinuance of therapy followed by an antidote or another drug in the same pharmacologic class might suggest an adverse event or lack of efficacy.

A major challenge for an MCO using MUE is the size of the population base exposed to the therapy in question and the number of prescribers and pharmacists involved in delivering targeted therapy. A large hospital may have 20,000 admissions yearly and approximately 100,000 patient days as a population pool that could be exposed to a medication, with well-defined medical and pharmacy staffs involved in the treatment process. A large MCO may have a million members, thousands of prescribers, and tens of thousands of pharmacies, creating procedural problems. However, this situation also creates a larger potentially treated population, allowing for a more thorough understanding of how a targeted therapy performs.

Another challenge is the matter of perspective. From whose perspective is the MUE focused? Often the interests, especially financial, of the payor and the health care provider regarding a given therapy are different. Although oral medications are generally of less concern in an institution because of their relatively lower costs, use, and risks when compared with parenteral agents, they are of major concern in the outpatient environment.

Perhaps the greatest challenge for both MCOs and institutions lies in demonstrating the value of a therapy. Value can be roughly defined as a quality outcome over cost, subject to different interpretations. An extension of the MUE process compares outcomes of different therapies and their associated costs. In this type of MUE, health care resource consumption rates can serve as a marker for clinical outcomes, with patient surveys serving as quality indicators. Historically, the only costs considered in the drug-use evaluation process have been acquisition costs. Integrated MCOs are now using total health care costs along with retrospective database research to create cost-effectiveness or cost-consequence comparisons of therapies.^{31,32}

Although differences exist between managed care organizations and institutions in how the MUE process is designed and used, most MUEs include justification for use, critical indicators, complication monitoring, and outcome assessment. Indeed, the goals of most MUE processes are virtually identical; the variance is in the location of the data.²

Special Considerations for Tramadol HCl Use in the Managed Care Setting

With regard to tramadol HCl, the MUE process and its results will likely be more valuable for an MCO than for an institution. A much larger patient population can be expected to be taking tramadol as a chronic maintenance medication. Additionally, more practice variation in the indication, dose, and monitoring criteria would be anticipated.

One issue for the managed care environment is that the frequency distribution analysis on patient diagnostic coding may reveal considerable off-label use. Rigidly defined MUE criteria typically would identify this as a problem. However, by incorporating outcome measures into the MUE process, a better assessment of the value of therapy can be determined. For example, given the multifaceted pharmacologic activities of tramadol HCl, it theoretically would be ideal for the treatment of fibrositis and fibromyalgia.³³ These conditions are seldom encountered in an institution, but are prevalent in the managed care environment and consume major health care resources. From the payor's perspective, the use of a single effective drug for treatment of fibrositis or fibromyalgia, rather than the use of drug combinations, is advantageous in terms of cost and compliance.

Equally important are the patients who may have an appropriate indication for tramadol HCl, or those who may be in an "at-risk" group from other therapies (e.g., NSAIDs), but who are not receiving tramadol HCl. This underutilization of appropriate therapy may have no direct impact on the pharmacy

budget but creates the potential for large costs on the medical side of the MCO. Because of the relatively larger patient-exposure factor (thousands of patient-months on tramadol HCl would not be uncommon in a managed care organization), data on the rates of complications identified in the MUE process would be enhanced. Prescriber selection bias (e.g., sicker patients receive newer therapy) could be accounted for in the data collected. These scenarios represent actual results of the MUE process in the managed care environment. They also represent opportunities for intervention by pharmacists to improve patient outcomes, decrease adverse drug reactions, and decrease total health care resource consumption and its concomitant costs, which create value for professional pharmaceutical services.

CONCLUSION

This MUE has been designed to provide a template for pharmacists to develop a comprehensive monitoring program for patients receiving tramadol HCl by evaluating use, safety, and therapeutic outcome. It may be modified as required to suit the specific needs of an individual health care organization or setting.

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