

Bridging health technology assessment with multicriteria decision analyses: field testing of the EVIDEM framework to support coverage decision for tramadol by a public health plan in Canada

EVIDEM

Mireille M Goetghebeur PhD,¹ Michèle Tony BSc*,¹ Monika Wagner PhD,¹ Hanane Khoury PhD,¹ Donna Rindress PhD,¹ Tina Papastavros BSc PharmD,² Paul Oh MD³

¹BioMedCom Consultants inc, Montréal, Québec Canada, ²Workplace Safety Insurance Board of Ontario, Toronto ³Toronto Rehabilitation Institute, Toronto, Ontario, Canada

Background

- Healthcare decisionmaking is a complex task that involves processing large amounts of disparate information, assessing quality of evidence, making value judgments and balancing conflicting ethical principles
- The mission of Health Technology Assessment (HTA) is “to assist and advice healthcare decisionmakers in defining health policies at all levels”¹; to fulfill this mission, in addition to clinical and economic aspects, HTA needs to address social, organizational, ethical and legal dimensions of health technologies²⁻⁴
- Current efforts to develop international standards for HTA reports^{5,6} point to the need for a structured format that can provide full access to the underlying evidence, thereby enhancing transparency and usability of the report to legitimize and improve decisions
- Multicriteria decision analysis (MCDA) is used to structure complex decision problems into a comprehensive set of components that can be considered separately; each component of decision is weighted (value elicitation) and options are scored with respect to each component to identify the preferred course of action⁷
- Applying MCDA principles, the EVIDEM framework proposes a standard set of components to structure healthcare clinical and policy decisionmaking; components are defined to reflect in an explicit manner the thinking process underlying assessment resulting in decisions⁸
- Application of the framework generates a structured HTA report consisting of distinct, clearly defined components that contain synthesized information highly relevant to decisionmakers
- Objective: Develop an EVIDEM HTA report to field test the framework by a public healthcare payer in Canada

Results

HTA report – “Lite version”

- The report was developed into a web-based prototype to include the two levels of data synthesis; full version includes details and hyperlinks to 67 references.

Overview

Drug class: non-conventional weak opioid with dual mechanism of action (weak mu-opioid effect of M1 metabolite, and weak monoaminergic effect)
Indication: moderate to moderately severe pain
Administration: tablets, once daily (slow-released tramadol – Ralivia, Tridural, Zytram); max 8 tablets daily (short-acting Tramacet)
Intervention duration: several days or more; head to head trials: 4 to 12 weeks
Comparator(s): placebo, NSAIDs, COX-2 inhibitors, opioids
Economic burden of illness: osteoarthritis - annual cost: \$3.59 billion; chronic low back pain - annual cost per patient (Netherlands): \$13,770; fibromyalgia - annual cost per patient: \$16,134

Quantitative considerations (MCDA Value Matrix)

Components	Highly synthesized information	Anchors for scoring
Disease impact		
D1 Disease severity	Chronic non-cancer pain includes nociceptive (tissue damage) and neuropathic (nerve pathology) pain; 37% of low back pain of neuropathic origin. Disabling condition interfering with activities of daily living (28% patients), work (lost income in 49% patients) and education. Associated with depression and/or anxiety (40% patients). [Assign score/See data details]	Min: Not severe Max: Very severe
D2 Size of population	Prevalence/Incidence: Canadian pain study 2004 (N=1055 in general population): 25% with chronic pain (88% moderate or severe); mean duration 9.8 years. [Assign score/See data details]	Min: Very rare disease Max: Common disease
Context of intervention		
C1 Clinical guidelines	Canadian Pain Society guidelines: <ul style="list-style-type: none">Chronic non-cancer pain (2002): no mention of tramadol - mild to moderate: 1st line non-opioid, 2nd line opioid (moderate to severe pain: switch to opioid earlier)Chronic neuropathic pain (2007): 3rd line tramadol/conventional opioid Other countries recommending tramadol for: <ul style="list-style-type: none">Osteoarthritis: 2nd line, USAChronic low back pain: 2nd line, USA and EuropeFibromyalgia: 2nd line, USA [Assign score/See data details]	Min: Not recommended Max: Strong recommendation
C2 Comparative interventions limitations	NSAIDs and COX-2 inhibitors: ceiling effect in pain reduction; organ damage after long term use (cardiac and renal; and gastric for NSAIDs) Opioids: not efficacious in pain of neuropathic origin; gastrointestinal (constipation, nausea, vomiting), respiratory (respiratory depression) and neurologic (dizziness, somnolence) side effects; risk of tolerance/dependence/abuse Specific to neuropathic pain: <ul style="list-style-type: none">Anticonvulsants (e.g., gabapentin, pregabalin): sedation, dizziness, ataxia, somnolence, confusionTricyclic antidepressants (e.g., amitriptyline): sedation, dry mouth, constipation, orthostatic hypotension, weight gainSNRIs (e.g., duloxetine, venlafaxine): nausea, dyspepsia, sweating, somnolence and insomniaSSRIs (e.g., fluoxetine): agitation, anxiety, sleep disturbance, tremor, sexual dysfunction and headache [Assign score/See data details]	Min: No or very minor limitations Max: Major limitations
Intervention outcomes		
I1 Improvement of efficacy/effectiveness	<i>Trials results obtained with WOMAC and other scales were recalculated to be expressed on a normalized scale from 0 (minimum improvement) to 100 (maximum improvement). If not mentioned, no significant difference</i> 5 Head to head randomized controlled trials (osteoarthritis, low back pain & other; 4 to 12 weeks; N =108 to 1001; 1 in Canada, 4 in USA): <ul style="list-style-type: none">Pain intensity reduction from baseline: tramadol: 15-24; diclofenac: 16; celecoxib: 26 (P=0.05 vs placebo); placebo: 19 (significant difference for all vs baseline)Pain intensity reduction after 6 hrs: tramadol: 21; codeine: 18 Placebo randomized controlled trials (Cochrane reviews): <ul style="list-style-type: none">Pain intensity reduction versus placebo:<ul style="list-style-type: none">- 8.5 (osteoarthritis, 3 trials, N= 92 to 307)- 10.8 (chronic low back pain, 3 trials, N= 254 to 336)Patients achieving 50% pain relief: 63% tramadol vs 37% placebo (neuropathic pain, 3 trials, N=67 to 127) [Assign score/See data details]	Min: Lower than comparators Max: Major improvement
I2 Improvement of safety & tolerability	Summary of common AEs (> 5% of patients in RCTs and frequency > twice of placebo in tramadol product monographs): <ul style="list-style-type: none">nausea: tramadol 10-24%; codeine 5-19%; diclofenac 11%somnolence: tramadol 7-18%; codeine 3-24%; diclofenac 8%dizziness: tramadol 7-24%; codeine 5-14%; diclofenac 18%constipation: tramadol 7-21%; codeine 10-21%; diclofenac 15%vomiting: tramadol 4-15%; codeine 1-7%; diclofenac 5%dry mouth: tramadol 5%, diclofenac 7%sweating: tramadol 1-15%; codeine 1%; diclofenac 0% Warnings tramadol: Seizure risk; anaphylactoid reactions, drug abuse, addiction and dependence; withdrawal symptoms; risk of overdose; increased intracranial pressure or head trauma; respiratory depression	Min: Lower than comparators Max: Major improvement
Drug abuse: 12 month study: tramadol 2.7%, NSAIDs: 2.5%; hydrocodone: 4.9% Surveillance study: tramadol: 0.5-2 cases/100,000 patients (over 10 years); oxycodone: at least 5/100, 000 cases (over 3 years) [Assign score/See data details]		

Components	Highly synthesized information	Anchors for scoring
I3 Improvement of patient reported outcomes	<i>Trials results obtained with WOMAC and other scales were recalculated to be expressed on a normalized scale from 0 (minimum improvement) to 100 (maximum improvement). If not mentioned, no significant difference</i> 3 Head to head RCTs (osteoarthritis studies; 6 to 12 weeks, N=108 to 1001, 1 in Canada, 2 in USA): <ul style="list-style-type: none">Physical function improvement from baseline: tramadol: 15-21, diclofenac: 15, celecoxib: 25 (P=0.05 vs placebo), placebo: 17Stiffness reduction from baseline: tramadol: 17, diclofenac: 18Quality of sleep improvement from baseline: tramadol: 10, diclofenac: 8 <i>(P<0.05 for all vs baseline; in 1 trial, no numbers reported for stiffness and quality of sleep but significance reported for tramadol/300 mg vs placebo and for celecoxib vs placebo) [Assign score/See data details]</i>	Min: Lower than comparators Max: Major improvement
Type of benefit		
T1 Public health interest	Risk of depression: The degree of depression improvement correlates with the amount of pain relief. Pain relief with tramadol may therefore have an impact on the risk of depression (no data available). [Assign score/See data details]	Min: No risk reduction Max: Major risk reduction
T2 Type of medical service	Tramadol produces symptom relief (20 points from baseline on a scale from 0 to 100) and may improve physical function, but does not cure pain. [Assign score/See data details]	Min: Minor service Max: Major service (e.g. cure)
Economics		
E1 Budget impact on health plan	Average daily cost per patient (based on historical claims data): Tramadol: \$2.24-2.27 (Zytram, Tridural, Ralivia) to \$2.91 (Tramacet) Comparators: <ul style="list-style-type: none">NSAIDs: \$0.11 to 0.80COX-2 inhibitor: \$1.58Opioids: \$0.67 to 6.61Antidepressants: \$0.61 to 8.77*SNRIs: \$2.66-8.77*Anticonvulsants: \$5.39 to 7.23* <i>*Based on maximum dose</i> Based on budget impact models for private drug plans Annual impact on budget for pain control (average % over 3 years): <ul style="list-style-type: none">Tridural model: +0.27%Ralivia model: -0.32%; highly sensitive to average dose of Ralivia (+2.08% for RCT doses; base case with US market doses) Drugs included in models: NSAIDs, COX-2 inhibitor, codeine, stronger opioids and Zytram; (plus meloxicam, acetaminophen in Ralivia model); (plus Tramacet in Tridural model) [Assign score/See data details]	Min: Substantial additional expenditures Max: Substantial savings
E2 Cost-effectiveness of intervention	Incremental cost (drug and adverse events) per patient over 6 months (based on cost-minimization study by Liedgens): <ul style="list-style-type: none">Tramadol vs NSAIDs only: +\$179Tramadol vs NSAIDs+ proton pump inhibitors (PPIs): -\$110 (savings)Tramadol vs NSAIDs+ histamine receptor antagonists (H2RAs): +\$66 Adverse events included for tramadol: constipation, nausea, vomiting, vertigo, somnolence, and other Adverse events included for NSAIDs: gastrointestinal distress, serious complications, ulcer, anemia from occult bleeding	Min: Not cost-effective Max: Highly cost-effective
E3 Impact on other spending	Impact on adverse events expenditures per patient over 6 months: (excluding drug cost, including all adverse events in Liedgens study) <ul style="list-style-type: none">Tramadol vs NSAIDs only: -\$567 (savings)Tramadol vs NSAIDs+ PPIs: -\$534 (savings)Tramadol vs NSAIDs+H2RAs: -\$574 (savings) <i>No data versus other comparators, no data on other spending (e.g. disability) [Assign score/See data details]</i>	Min: Substantial additional spending Max: Substantial savings
Quality of evidence		
Q1 Adherence to requirements of decision-making body	Not applicable for case study [Assign score/See data details]	Min: Low adherence Max: High adherence
Q2 Completeness and consistency of reporting evidence	Clinical data: 5 trials: overall consistent reporting within studies but some issue in completeness of reporting including: no numerical data for efficacy (1 trial) or safety (1 trial), type of analysis unclear (1 trial), data collection schedule unclear (1 trial); Economic evaluation (1 cost-minimization study): overall consistent reporting within study but some issues in completeness of reporting including: no disaggregated data regarding resource utilization and associated costs, sensitivity analyses data reported for only one parameter [Assign score/See data details]	Min: Many gaps/inconsistent Max: Complete and consistent
Q3 Relevance and validity of evidence	Clinical data: 5 trials: a number of issues regarding validity and relevance including: short trial duration for chronic treatment (4 trials ≤ 6 weeks), data mostly in older osteoarthritis patients, most data for short-acting tramadol (3 trials), interpretation of results difficult (2 trials), high attrition rate (> 20% in 3 trials); efficacy measure (4-6 hrs after treatment) not relevant for chronic pain (2 trials) Economic evaluation (1 cost-minimization study): a number of issues regarding validity and relevance including: Dutch setting; only NSAIDs as comparators; only adverse events considered (not consequences of these); short duration for chronic disease (6 months); only medical costs considered [Assign score/See data details]	Min: Low relevance / validity Max: High relevance / validity

Methodology

- Tramadol for chronic non-cancer pain was selected as a relevant case study for the Canadian public healthcare payer
- An extensive analysis of the published literature and proprietary data was performed to identify relevant data for each component of the framework regarding disease impact, context of intervention, intervention outcomes, type of benefit, economics, quality of evidence, ethical framework, and other system-related components
- Quality of evidence with respect to “completeness and consistency of reporting” and “relevance and validity of evidence” was assessed for clinical data and the economic evaluation
- To produce a structured HTA report, the data collected was synthesized using EVIDEM tools (at 2 levels: full and ‘lite’ version) and organized into the framework to inform:
 - 15 components of decision (quantifiable from a universal standpoint) organized into the MCDA Value Matrix to estimate the “intrinsic value” of the intervention;
 - 6 system-related components of decision (non-quantifiable from a universal standpoint) organized into the Extrinsic Value Tool to explore qualitative considerations; data is provided to stimulate reflection but needs further input from decisionmakers.
- The framework was presented to the public payer drug advisory committee and feedback was collected from its members.

Qualitative considerations (Extrinsic Value Tool)

Components	Highly synthesized information	Impact & comments
Ethical framework*		
E1 Goals of healthcare – utility	Goal of healthcare: maintain normal functioning. Pain has a major impact on functioning and relieving pain is an ethical duty. [Assign score/See data details]	Negative/None/Positive
E2 Opportunity costs – efficiency*	Maximizing impact on health for a given level of resources at: Patient level: tramadol offers another option for pain relief but is more expensive than most other analgesics Population level: Interest in using resources to treat underlying disease/condition rather than symptoms [Assign score/See data details]	
E3 Population priority & access – fairness*	Prioritize worst off: Chronic pain has major ramifications for patients, family and society. Tramadol provides another option to tackle widespread undertreated chronic pain Treat like cases similarly: Should chronic non-cancer pain be treated differently than cancer pain? Access to care/treatment: barriers for prescribing opioids (fear of addiction and of regulatory scrutiny), critical in general practice [Assign score/See data details]	
Other system-related components		
O1 System capacity and appropriate use of intervention	Risk of abuse of opioids and difficulty to control abuse; standardized guidelines to limit abuse (mainly ensure non-opioid failed, single pharmacy/doctor and comprehensive follow-up) not always applicable in busy practices or complex cases Abuse rates: lower for tramadol than for hydrocodone [Assign score/See data details]	
O2 Stakeholder pressures	Canadian Pain Society: clinician pressures on Health Canada to keep tramadol out of the controlled drug schedule on the basis that it is a good option for moderate pain and associated with less abuse than other opioids Currently, tramadol is not scheduled in Canada [Assign score/See data details]	
O3 Political/historical context	WHO committee concluded that, based on low level of abuse, there was not sufficient evidence to justify a review. WHO reports some evidence of smuggling and diversion of tramadol but no evidence of illicit manufacture CEDAC recommendation: do not list; Other workplace insurance boards: reimbursement of tramadol case specific [Assign score/See data details]	
Ethical framework based on three principles: when conflicting principles, identify trade-offs and legitimize decision by engaging a broad range of stakeholders & explaining decision; legitimizing decision is key ^{10,11} to providing accountability for reasonableness ^{12,13}		

Feedback from committee

- Committee members indicated that most of the components of decision considered in the MCDA Value Matrix are relevant in their context. Including other considerations, such as patient preferences and importance of disease to population affected was suggested
- Some members voiced concern about the amount of work involved in developing the HTA report
- Several participants indicated that the framework is a good point of departure to help lead group discussion and to ensure systematic consideration of important elements that may affect decisionmaking process
- To cite one committee member: “EVIDEM is a good tool in the sense that it forces each member to think and weight aspects that otherwise would not have been considered”

Discussion and conclusion

- The EVIDEM framework layout is an innovative and concise way to present key data necessary to orientate decisionmaking and to efficiently communicate and share HTA among its users; as for any HTA, the data presented is limited by evidence available
- The framework is a practical tool which supports transparency of data and consistency in the decision process by prompting explicit consideration of each component of decision
- Creation of a structured HTA report is the first step in the application of the framework to support healthcare decisionmaking; full testing of the framework, including collection of weights and scores and calculation of MCDA estimate is ongoing
- Further field testing and instrument validation is needed to collaboratively advance this framework and contribute to more transparent and efficient HTA and healthcare decisionmaking

Acknowledgments

We wish to acknowledge the contributions of the members of the Drug Advisory Committee of the Workplace Safety Insurance Board (WSIB) who participated in this beta-testing. Internal sources of support for the study were provided by the WSIB and BioMedCom. *Michèle Tony received a MSc grant from BioMedCom.

References

- Giovagnoni A et al. Radiol Med 2009;114(5):673-91.
- INAHTA - HTA Resources. 2010. <http://www.inahta.org/HTA/>
- Velasco GM et al. Health Policy 2010;94(3):196-202.
- Johri M, Lehoux P. Int J Technol Assess Health Care 2003;19(1):179-93.
- EU-netHTA work package 4 team. HTA core model for medical and surgical interventions. 2007.
- Hailey D. Int J Technol Assess Health Care 2003;19(1):1-7.
- Baltussen R, Niessen L. Cost Eff Resour Alloc 2006;4:14.
- Goetghebeur MM et al. BMC Health Serv Res 2008;8(1):270.
- World Health Organization. 2004. <http://www.who.int/ethics/Guidance%20on%20Ethics%20and%20HIV.pdf>
- Gruskin S et al. Am J Public Health 2008;98(9):1573-7.
- Persad G et al. Lancet 2009;373:423-31.
- Daniels N. J Urban Health 1999;76(2):176-91.
- Daniels N. Am J Bioeth 2001;1(2):2-16