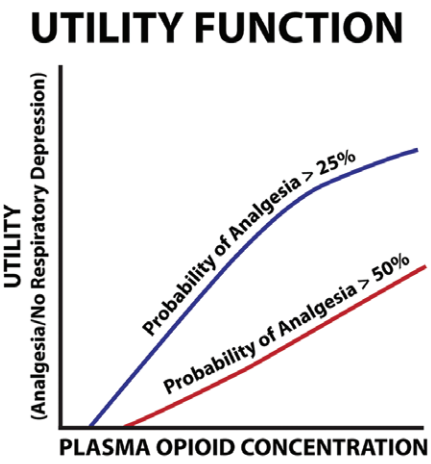
μ-Opioid Receptor Agonists

Do They Have Utility in the Treatment of Acute Pain?

Thomas K. Henthorn, M.D., Susan K. Mikulich-Gilbertson, Ph.D.

IN this issue of Anesthesiology, Roozekrans *et al.*[1] have revisited the utility function to emphasize the balance between therapeutic efficacy and toxicity of opioids. They reanalyze data from three previously published studies of the analgesic and respiratory depressant effects of alfentanil[2–4] to determine "utility" from the perspective of producing analgesia without significant respiratory depression. Further exploration of the theoretical underpinnings of opioid utility is particularly *a propos* given the escalating number of respiratory depression deaths due to the opioid epidemic[5,6] coupled with the most salient finding of the pharmacokinetic–pharmacodynamic analysis of Roozekrans *et al.*[1]: that the EC_{50} for alfentanil analgesia exceeds the EC_{50} for respiratory depression. This is far from an encouraging therapeutic index. It is, therefore, worth comparing this new work with prior operationalizations of opioid utility while reflecting on how the utility function can evolve and become a more central concept to clinicians, pharmacologists, and public health officials.



"Can the concept of the utility function help us understand the benefit to risk relationship of a pure μ-opioid receptor agonist…?"

The Leiden group first introduced the utility function to the anesthesiology literature in 2013.[7] This publication prompted an in-depth discussion by Kharasch and Rosow[8] of the origins of the utility function and the potential of this important new tool to "intensify the vigor" of the evaluation of the dose-response relationship.

The utility function is not a defined equation or computation, but more generally, a determination of value that accounts for both "good" and "bad" outcomes. In its original form the utility function (UF) simplistically computes economic value as:

$$UF = profit - loss$$

Sheiner and Melmon[9] translated this into more medical terminology as:

$$UF = benefit - harm$$

They posited a utility function for antihypertensive drugs as the value of the benefit of drugs that lower blood pressure minus the cost of harm from antihypertensive drug toxicity in order to determine whether lowering blood pressure with these drugs has utility in a public health sense.

Although drug effect data are typically continuous or ordinal (*e.g.*, minute ventilation), that information is dichotomized into designations of "benefit" (yes/no) and "harm" (yes/no) to place these "good" and "bad" outcomes on similar scales in order to compute a utility function. Designations or thresholds for "yes" *versus* "no" may appear somewhat arbitrary; indeed, Roosekrans *et al.*[1] evaluated successful analgesia from alfentanil (*i.e.*, benefit) with two different thresholds: a 25% and a 50% increase in tolerated electrical current.

The nonlinear mixed effects analysis introduced by Sheiner and Beal[10] provides a mechanism for estimating parameters of pharmacokinetic–pharmacodynamic models in a population and describing the inter- and intraindividual variability among individuals. From these estimates, large-scale population simulations of continuous measures of beneficial and harmful effects can then be conducted. These simulated results can be dichotomized into indicators of benefit and harm so that the probabilities of the benefit and harm outcomes comprising utility can be calculated at various drug concentrations and times.

Using this approach, Cullberg *et al.*[11] evaluated whether the probability of anticoagulant therapy preventing clots (benefit) outweighed the probability of producing unwanted

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bleeding (harm). They modeled the relationship between the pharmacokinetic–pharmacodynamics of ximelagatran and the probabilities of clot regression and bleeding events with nonlinear mixed effects analysis. The utility function was expressed as the difference between the probabilities of clot regression and a bleeding event ranging from −1 to +1 with 0 indicating no utility. They found positive utility across a wide range of drug exposure. Significantly, the authors moved the conversation from evaluating utility of outcomes at a "global" level, as proposed by Sheiner and Melmon,[9] to evaluating utility from events or processes measured during a single multicenter clinical trial. This allows clinical pharmacologists to begin the conversation about the utility of pharmacotherapy at an earlier stage.

In Leiden, Yassen *et al.*,[12] took Cullberg's approach[11] of computing a utility function from process variables in a clinical trial into a preclinical study in rats to compute a fentanyl utility function and a buprenorphine utility function by subtracting the respective probabilities of each producing respiratory depression from the respective probabilities of each producing analgesia. At relevant concentrations the buprenorphine utility function was positive while the fentanyl utility function was negative, indicating a superior effectiveness/safety profile for buprenorphine compared to fentanyl in this rat model.

Subsequently, Boom *et al.*,[7] conducted a rigorous population pharmacokinetic–pharmacodynamic clinical trial of the analgesic and respiratory effects of fentanyl in healthy male volunteers. They used the inter- and intraindividual variability estimates of their pharmacokinetic–pharmacodynamic analyses to simulate data for 10,000 individuals. From these simulations they calculated probabilities of achieving at least a 50% improvement in pain tolerance, and a greater than 50% reduction in ventilatory response to carbon dioxide across time following fentanyl administration and across observed concentrations. Unlike ximelagatran and drugs used to treat hypertension, the utility function for fentanyl was largely negative. While these findings would not be a surprise to paramedics and police officers treating illicit fentanyl overdoses in the street, most anesthesiologists perceive great utility in fentanyl and would quibble with this utility function definition. Boom *et al.*,[7] cautioned that utility functions were still experimental, requiring validation, refinement, and more clinically relevant definitions.

In their present work, Roozekrans *et al.*[1] have made significant advancements. They have further validated the general approach, considering a different opioid—alfentanil—and incorporating additional datasets for the population pharmacokinetic–pharmacodynamic analyses. They demonstrate how utility functions can be used to evaluate concentrations at which a specific drug or a set of drugs (*e.g.*, multimodal analgesia[13]) improves the probability of attaining sufficient efficacy without unsafe or unwanted toxicity in human studies. Their expanded definitions of both analgesia and respiratory depression beyond those in the Boom *et al.*[7] and Yassen *et al.*[12] studies can more easily be applied to different clinical situations, *e.g.*, opioids used as adjuncts for general anesthesia or for outpatient pain therapy. However, these constructs may fall into the common trap of using process variables as surrogates for relevant outcomes,[14,15] such as equating a 50% decrease in minute ventilation while breathing high concentrations of carbon dioxide with actual morbidity or mortality from respiratory depression.

The probabilities underlying the utility functions recommended by Roozekrans *et al.*[1] differ from those of their previous work. Table 1 illustrates how counts and probabilities (P) of two conditions can be tabulated in a 2 × 2 table. Each cell contains the observed count and the *joint probability* of each condition combination, *e.g.*, for a specific concentration of drug. The first cell denotes P(Benefit AND No Harm) computed as number of cases where analgesia greater than 0.5 and respiratory depression less than 0.5 (n_1) is divided by total cases (N). The sum of cells comprising each row and separately each column, denotes the *marginal probability* of that condition, *e.g.*, for the first row:

$$P\left(Benefit\ AND\ No\ Harm\right) + P\left(No\ Benefit\ AND\ No\ Harm\right) = P\left(No\ Harm\right)$$

This marginal probability of no harm, then, is the probability that a drug does no harm regardless of whether it provides benefit. Whereas predecessors have computed utility

Table 1. Tabulation of Counts and/or Probabilities (P) of Each Condition in a 2 × 2 Table

Condition	Benefit	No Benefit	
No Harm	n_1	n_2	$\frac{n_1+n_2}{N} = P\left(No\ Harm\right)$
	$\frac{n_1}{N} = P\left(Benefit\ AND\ No\ Harm\right)$	$\frac{n_2}{N} = P\left(No\ Benefit\ AND\ No\ Harm\right)$	
Harm	n_3	n_4	$\frac{n_3+n_4}{N} = P\left(Harm\right)$
	$\frac{n_3}{N} = P\left(Benefit\ AND\ Harm\right)$	$\frac{n_4}{N} = P\left(No\ Benefit\ AND\ Harm\right)$	
	$\frac{n_1+n_3}{N} = P\left(Benefit\right)$	$\frac{n_2+n_4}{N} = P\left(No\ Benefit\right)$	$N = n_1+n_2+n_3+n_4$

functions as the difference between marginal probabilities for their respective definitions of benefit and harm[7,11,12]:

$$UF = P(Benefit) - P(No\ Harm),$$

Roozekrans *et al.*[1] denote a utility function for the most desirable outcome as the joint probability of benefit with no harm occurring:

$$UF = P(Benefit\ AND\ No\ Harm).$$

They also denote a utility function for the least desirable outcome as the joint probability of no benefit with harm occurring:

$$UF = P(No\ Benefit\ AND\ Harm);$$

calling this a utility function is misleading in that it is actually the probability of the complete absence of utility.

The Centers for Disease Control and Prevention has recently issued a guideline for the prescription of opioids, mainly for primary care physicians treating chronic pain.[16] This guideline recognizes that chronic pain treatment often begins with acute pain treatment and for the treatment of the latter the following statements are offered: "when opioids are used for acute pain, clinicians should…prescribe the lowest effective dose…(and) incorporate into the management plan strategies to mitigate risk." Can the concept of the utility function help us understand the benefit to risk relationship of a pure μ-opioid receptor agonist, such as alfentanil, which is normally administered in the operating room or intensive care? Also, how might we understand the meaning of "lowest effective dose," which is not explicitly definable in a pharmacologic sense?

From a safety standpoint, we could restrict our evaluation to the condition of no significant respiratory depression (table 1, No Harm row) and examine the probability of obtaining analgesia (Benefit) in that group, *i.e.*, the conditional probability of benefit given no harm, denoted as:

$$P(\text{Benefit} \mid \text{No Harm}) = \frac{n_1}{n_1 + n_2}$$

To illustrate, we used the alfentanil pharmacokinetic–pharmacodynamic parameter estimates, including the inter- and intraindividual variability, from Roozekrans *et al.*[1] to simulate a 90-min infusion of alfentanil (30 μg · kg^{-1} · min^{-1}) in 200 patients with 20 simulated time points during 5 h to simulate alfentanil plasma concentration-effect relationships for both analgesia and respiratory depression. After excluding all alfentanil concentration analgesic-respiratory depression effect pairs with 50% respiratory depression or more (row 2, table 1) the probability of attaining 25% and 50% analgesia for the remaining effect pairs in which respiratory depression was less than 50% was calculated up to the EC_{50} for respiratory depression (80 ng/ml; figure 1.)

Some analgesia (*e.g.*, 25% increase in tolerated pain) without respiratory depression is indeed likely, but begins to plateau *versus* concentration at a probability of 0.7 and 60 ng/ml. This seems to fit the Centers for Disease Control and prevention concept of lowest effective dose but contradicts a prevalent perioperative acute pain culture of using opioids alone to reduce pain scores to 4 of 10 or lower. To reach a score of 4 of 10 or lower often requires a 50% improvement in analgesia. Figure 1 shows that after eliminating data with significant respiratory depression, the probability of getting a 50% reduction in pain score is only approximately 0.4. Pushing higher concentrations to increase the probability would require crossing the EC_{50} for respiratory depression and be inconsistent with "mitigating risk." Roozekrans *et al.*[1] provide more complete figures, which do not segregate on the marginal condition of No Harm (table 1, top row), and in which the joint probability (or utility) of analgesia AND no significant respiratory depression are shown for a much larger alfentanil concentration range.

Thus, examining therapeutic utility in terms of probabilities provides useful insights and challenges current practice. The probability of a pure μ-opioid receptor agonist achieving a 25% reduction in pain score without causing respiratory depression is only approximately 0.7, even in drug-free, healthy, young subjects. Achieving a 50% reduction in pain without significant respiratory depression is a less than 50:50 proposition. These findings highlight the need for new strategies for treating acute and chronic pain. Utility functions that incorporate different estimates of probabilities for

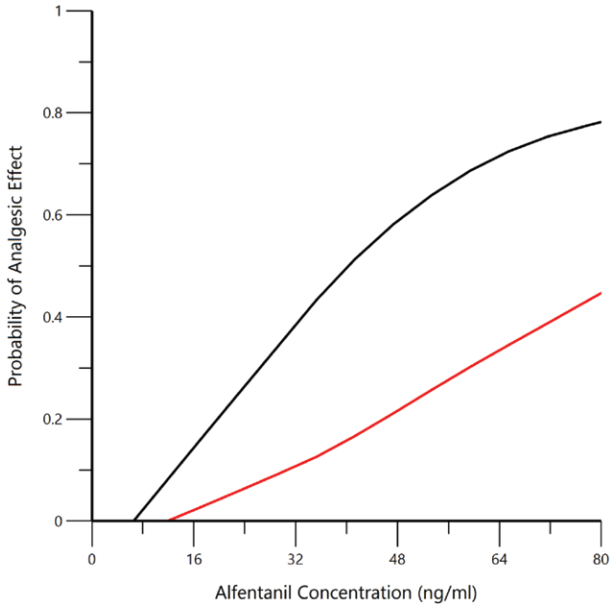

Fig. 1. Probability of achieving a 25% increase in pain tolerance (*black line*) or 50% increase in pain tolerance (*red line*) without significant respiratory depression *versus* alfentanil plasma concentration. The upper limit of alfentanil plasma concentration is 80 ng/ml as the EC_{50} for respiratory depression is 82 ng/ml.

achieving successful pain relief while minimizing risk can facilitate the evaluation of new pain management strategies.

Competing Interests

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Correspondence

Address correspondence to Dr. Henthorn: thomas.henthorn@ucdenver.edu

References

1. Roozekrans M, van der Schrier R, Aarts L, Sarton E, van Velzen M, Niesters M, Dahan A, Olofsen E: Benefit *versus* severe side effects of opioid analgesia: Novel utility functions of probability of analgesia and respiratory depression. Anesthesiology 2018; 128:932–42
2. Olofsen E, Romberg R, Bijl H, Mooren R, Engbers F, Kest B, Dahan A: Alfentanil and placebo analgesia: No sex differences detected in models of experimental pain. Anesthesiology 2005; 103:130–9
3. Roozekrans M, Olofsen E, van der Schrier R, van Gerven J, Peng S, McLeod J, Dahan A: Reversal of opioid-induced respiratory depression by BK-channel blocker GAL021: A pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Clin Pharmacol Ther 2015; 97:641–9
4. Roozekrans M, Olofsen E, van der Schrier R, Boom M, Mooren R, Dahan A: Doxapram-mediated increase in cardiac output reduces opioid plasma concentrations: A Pharmacokinetic/Pharmacodynamic-Pharmacokinetic/Pharmacodynamic modeling study in healthy volunteers. Clin Pharmacol Ther 2017; 102:115–22
5. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN: Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. Pain 2015; 156:569–76
6. Psaty BM, Merrill JO: Addressing the opioid epidemic—Opportunities in the postmarketing setting. N Engl J Med 2017; 376:1502–4
7. Boom M, Olofsen E, Neukirchen M, Fussen R, Hay J, Groeneveld GJ, Aarts L, Sarton E, Dahan A: Fentanyl utility function: A risk-benefit composite of pain relief and breathing responses. Anesthesiology 2013; 119:663–74
8. Kharasch ED, Rosow CE: Assessing the utility of the utility function. Anesthesiology 2013; 119:504–6
9. Sheiner LB, Melmon KL: The utility function of antihypertensive therapy. Ann NY Acad Sci 1978; 304:112–27
10. Sheiner LB, Beal SL: Evaluation of methods for estimating population pharmacokinetics parameters. I. Michaelis-Menten model: Routine clinical pharmacokinetic data. J Pharmacokinet Biopharm 1980; 8:553–71
11. Cullberg M, Eriksson UG, Wåhlander K, Eriksson H, Schulman S, Karlsson MO: Pharmacokinetics of ximelagatran and relationship to clinical response in acute deep vein thrombosis. Clin Pharmacol Ther 2005; 77:279–90
12. Yassen A, Olofsen E, Kan J, Dahan A, Danhof M: Pharmacokinetic-pharmacodynamic modeling of the effectiveness and safety of buprenorphine and fentanyl in rats. Pharm Res 2008; 25:183–93
13. Savarese JJ, Tabler NG Jr: Multimodal analgesia as an alternative to the risks of opioid monotherapy in surgical pain management. J Healthc Risk Manag 2017; 37:24–30
14. Fisher DM: Surrogate end points. Are they meaningful? Anesthesiology 1994; 81:795–6
15. Fisher DM: Surrogate outcomes: Meaningful not! Anesthesiology 1999; 90:355–6
16. Frieden TR, Houry D: Reducing the risks of relief–The CDC opioid-prescribing guideline. N Engl J Med 2016; 374:1501–4