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The Application of Failure Modes and Effects Analysis Methodology to Intrathecal Drug Delivery for Pain Management

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Objective: This study aimed to utilize failure modes and effects analysis (FMEA) to transform clinical insights into a risk mitigation plan for intrathecal (IT) drug delivery in pain management.

Methods: The FMEA methodology, which has been used for quality improvement, was adapted to assess risks (i.e., failure modes) associated with IT therapy. Ten experienced pain physicians scored 37 failure modes in the following categories: patient selection for therapy initiation (efficacy and safety concerns), patient safety during IT therapy, and product selection for IT therapy. Participants assigned severity, probability, and detection scores for each failure mode, from which a risk priority number (RPN) was calculated. Failure modes with the highest RPNs (i.e., most problematic) were discussed, and strategies were proposed to mitigate risks.

Results: Strategic discussions focused on 17 failure modes with the most severe outcomes, the highest probabilities of occurrence, and the most challenging detection. The topic of the highest-ranked failure mode (RPN = 144) was manufactured monotherapy versus compounded combination products. Addressing failure modes associated with appropriate patient and product selection was predicted to be clinically important for the success of IT therapy.

Conclusions: The methodology of FMEA offers a systematic approach to prioritizing risks in a complex environment such as IT therapy. Unmet needs and information gaps are highlighted through the process. Risk mitigation and strategic planning to prevent and manage critical failure modes can contribute to therapeutic success.

Keywords: Chronic pain, intrathecal drug delivery, intrathecal pump, intrathecal therapy, safety

Conflict of Interest: Stanley P. Fisher, MD, serves as an advisor for Mallinckrodt. Michael F. Saulino, MD, PhD, is on the speaker's bureau and serves as a clinical investigator for Jazz Pharmaceuticals and Medtronic, Inc. He is also a clinical investigator for Mallinckrodt and a consultant for SPR Therapeutics. Teresa Patel, PharmD, is an employee of Mallinckrodt.

INTRODUCTION

Infusion of analgesics into the intrathecal (IT) space has become more common since its first use for chronic pain management in the 1980s (1). This invasive therapy, which involves surgical implantation of a pump, is usually reserved for patients with pain refractory to systemic analgesics (1). The potential for serious adverse events (AEs) must be weighed against the analgesic benefits of IT drug delivery, and in appropriate patients, the choice of optimal products or combinations may be challenging. The associated AEs as well as the intricacies of the therapy may prevent initiation or utility of IT drug delivery in patients who could otherwise benefit. Although panels of experts have published best practice or consensus guidelines in an effort to mitigate risk (1,2), evaluation of how risk factors may affect the decision to use IT therapy and practitioners' risk tolerance for these barriers should be examined.

The failure modes and effects analysis (FMEA) approach is a qualitative analysis method to identify potential systematic failures and their effects (3). Through the mitigation of "failures," associated risks can be minimized and IT patient care improved. In automotive and aviation industries, FMEA is widely accepted (4,5) for preventing product or process defects, improving safety, and enhancing customer satisfaction (3). In the medical device industry, FMEA has been incorporated into International Organization for Standardization 9000 standards (e.g., Good Manufacturing Practice) to decrease product liability resulting from manufacturing (4). The Joint

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Table 1. Failure Modes and Effects Analysis Scale for Severity, Probability, and Detection.

Severity scale (scale 1 [least severe] to 10 [most severe] for each effect)

Minor (1)	Low (2–3)	Moderate (4–6)	High (7–8)	Very High (9–10)
It is unreasonable to expect that the minor nature of this failure will have any noticeable effect on the patient or choice of therapy. The patient will most likely not be able to detect the failure.	Because of the nature of this failure, the patient experiences only slight deterioration or a slight inconvenience with therapy.	The failure causes some patient dissatisfaction, which may include discomfort or deterioration. This may result in unscheduled clinic visits or change of therapy.	Dissatisfaction results from the nature of the failure, such as increased hospital stay. It may result in serious disruption to therapy.	The failure affects safety or increases mortality. It may endanger the life of the patient.

Probability scale (scale 1 [least frequent] to 10 [most frequent] for the occurrence)

Remote (1)	Very Low (2)	Low (3–5)	Moderate (6–7)	High (8–9)	Very High (10)
Failure is unlikely; this failure was never encountered.	Only a few isolated failures were ever encountered or reported.	Isolated failures have been encountered.	Occasional minor failures have been encountered.	Failure is often encountered.	Failure is almost inevitable.

Detection scale for occurrence (scale 1 [always detected] to 10 [never detected] for each occurrence)

Very High (1–2)	High (3–4)	Moderate (5–6)	Low (7–8)	Very Low (9)	No Detection (10)
It is almost certain to detect the failure mode.	There is a good chance of detecting the failure mode.	One may detect the existence of the failure mode.	There is a poor chance of detecting the existence of the failure mode.	One probably will not detect the existence of the failure mode.	The existence of the failure mode will not or cannot be detected.

Commission has recommended the use of FMEA as a proactive risk management method to improve quality and patient safety in healthcare (6). As a result, hospitals have used FMEA to evaluate new technologies (e.g., smart IV infusion pumps [7], stereotactic radiosurgery using CyberKnife® [8]) and minimize failures when human behavior and machine logic may be in conflict. Clinical decisions regarding IT therapy inherently utilize a risk mitigation thought process because of the potential for harm with IT therapy. An FMEA is a reasonable method to systematically identify risks associated with IT analgesia and develop strategies to address them. This method of analysis has not previously been applied to IT therapy.

The goal of this study was to evaluate failure modes that may be obstacles to the adoption of IT therapy. To this end, a group of clinicians conducted an FMEA during an advisory board on pain management. Additional goals of this group were to develop strategies to improve IT therapy adoption, reduce associated safety risks, and address deficiencies in current research.

METHODS

The FMEA process focuses on causes of undesirable outcomes and opportunities for preventing negative effects. Failure modes (e.g., rationales for not administering IT therapy, issues encountered with IT therapy or as a result of not administering IT therapy) and their effects were identified on the basis of previously gathered expert insights. To delineate concerns across treatment decisions and processes, the failure modes for initiation and maintenance of therapy were separated. Failure modes on manufactured versus compounded products, single versus combination medications, and reimbursement of therapy were combined under "product selection" to consolidate discussion of unmet needs in the market. In addition, the etiology of pain was classified as cancer versus noncancer because treatment goals that are based on patients' life expectancy and quality of life goals differ between these patient types.

Ten U.S. clinicians from various medical specialties were recruited to a one-day advisory board meeting. Of the ten participants, eight were anesthesiologists, one was a neurologist, and one was a physiatrist. Two physicians treated a variety of pain types, three focused on cancer pain, three on noncancer pain, and two on pain associated with spasticity; practice settings ranged from academic centers (60%) to private practice/hospitals (40%). The group has >140 years of combined medical practice experience, and altogether the advisors manage >1200 patients with IT pumps each year. The participants received background materials on FMEA methodology before the meeting.

The FMEA process was divided into two parts; in the first, instruction on FMEA concepts and scoring was provided. An FMEA facilitator (who was not included in the ten-member panel and did not provide scores) assisted with the meeting and answered methodology questions to ensure that all participants were clear on the process. To further aid in the process, one of the advisory board participants served as the meeting moderator and shared his ratings along with clinical examples for each failure mode. In addition to verbal directions on scoring, a guide (Table 1) was provided that defined the scales for failure modes as follows:

- Severity score (S): 1 to 10 scale from least to most severe
- Probability score (P): 1 to 10 scale from least to most probable
- Detectability score (D): 1 to 10 scale from most to least detectable

Participants provided ratings for 37 failure modes on FMEA work sheets. Ratings were based on each participant's practice setting; if a failure mode was not applicable to the practice or patient

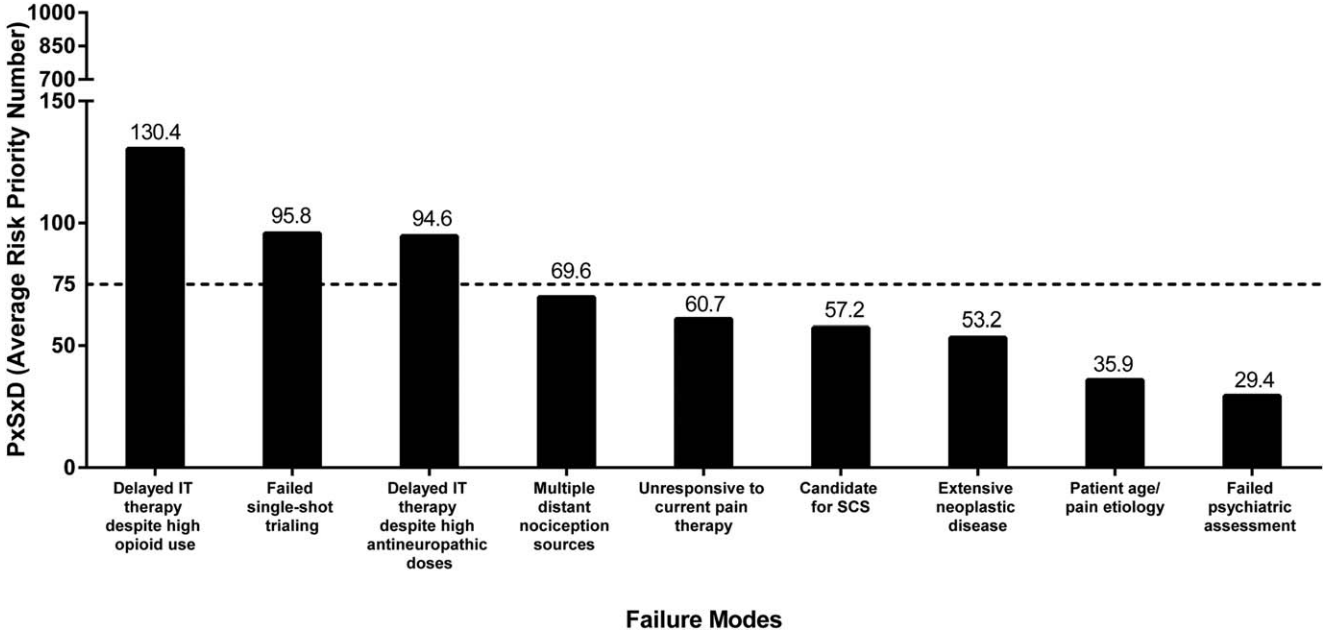

Figure 1. Patient selection for therapy initiation—efficacy. Abbreviations: IT, intrathecal; PxSxD, prevalence score multiplied by severity score multiplied by detectability score; SCS, spinal cord stimulation.

population, a low score (1–2) was assigned. Once all failure modes were scored, a risk priority number (RPN) was calculated by multiplying the three averaged scores (i.e., PxSxD) for each failure mode. Failure modes with the highest RPNs were those with the most severe outcomes, the highest probabilities of occurrence, and/or the most challenging detection.

The RPN alone lacks clinical meaning because each failure mode has its own effect and the effects are not directly comparable (3). The score is not designed to assess interrater response and does not predict specific consequences of each failure mode. Additionally, RPNs should not be considered ordinal functions (e.g., an item with an RPN that is twice as large as that of another item should not be considered twice as severe or important). However, the RPNs can be ranked to identify top priorities for risk mitigation, which is the focus of this methodology. The mitigation of undesirable outcomes was more important than the quantification of outcomes in this study.

The second part of the meeting involved identification of solutions for high-priority failure modes. Blinded individual scores were displayed on a spreadsheet along with the average severity, probability, detection, and RPN scores for each failure mode. An FMEA methodology efficiently identifies elements that cause systematic failures because 80% of the total RPN for an FMEA comes from just 20% of the potential failures and effects (i.e., the 80/20 rule); hence, an RPN threshold was chosen in order to focus on the most impactful failure modes (3). In this analysis, failure modes with an RPN ≤ 75 (after rounding and eliminating ending zeros) were not prioritized for further discussion. The group discussed the 17 failure modes with the highest RPNs (>75), which constituted 46% of the 37 RPNs in this FMEA, in an effort to be reasonably comprehensive. The participants' opinions and proposed solutions regarding these high-ranking failure modes are summarized in the Results section.

RESULTS

Each participant scored all failure modes. Severity was assigned the highest scores (8–10) most frequently, and ratings for probability and detectability were inconsistent among clinicians. Figures 1–5 display average RPNs along with the threshold (i.e., RPN > 75) required for discussion of the failure modes during the meeting. The following sections describe scores for and dialogue around each failure mode with an average RPN > 75. Results are organized into categories (i.e., patient selection for therapy initiation—efficacy, patient selection for therapy initiation—safety, patient safety during IT therapy, and product selection for IT therapy).

Patient Selection for Therapy Initiation—Efficacy

The failure modes for patient selection involve major issues that prevent optimal therapy. Nine failure modes were scored in this category, and three reached an RPN > 75 (Fig. 1; Supporting Information Table S1). The effects of delaying IT therapy despite high doses of opioids (e.g., morphine, hydrocodone) or neuropathic pain medications (e.g., gabapentin, pregabalin) had a moderate to high severity rating (S = 5.3–7.1) that elevated the overall RPNs for these failure modes. The probability of delayed IT therapy depended on the referral system, which differed among institutions and practices. Earlier referral to pain specialists may lead to faster IT therapy initiation. Delays may be caused by referring physicians' lack of education or time as well as by concerns about AEs.

Issues around use of a single-shot trial prior to IT drug infusion produced much debate. This failure mode (failed single-shot trial) had moderate scores for severity (S = 5.7) and probability (P = 4.0) but produced the highest value for difficulty of detection (D = 4.2) within this category. Trialing methodology (percutaneous IT versus percutaneous epidural) and trialing dose varied across practices. The correlation between single-shot trialing and longer-term (six months) IT infusion efficacy and safety has not been firmly established (1). Bolus dosing in single-shot epidural trials does not mimic IT infusion because of variable pharmacodynamics and fluid dynamics (1). As a result, patients who fail a single-dose trial may still be good candidates for IT therapy; however, no panel member would recommend placing an IT device in these patients. Further complicating the interpretation of single-shot trial results, pain relief during

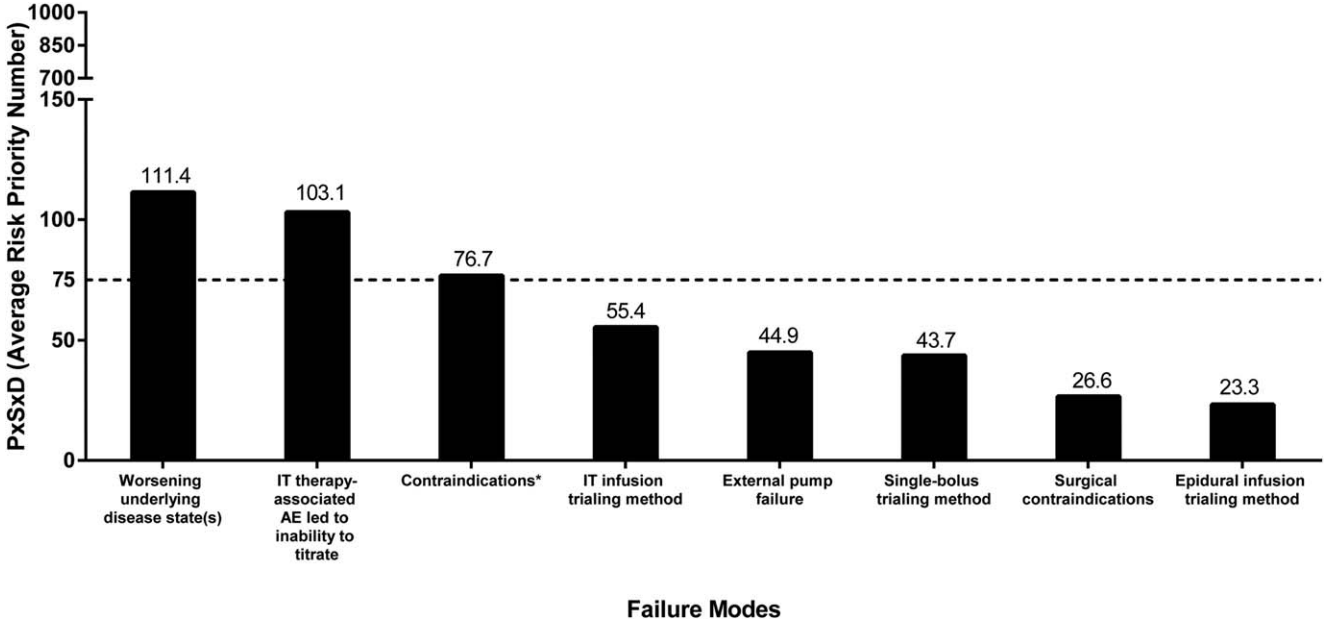

Figure 2. Patient selection for therapy initiation–safety. *Anticoagulants, antiepileptics, benzodiazepines, antiplatelet medications. Abbreviations: AE, adverse event; IT, intrathecal; PxSxD, prevalence score multiplied by severity score multiplied by detectability score.

trialing may be a placebo response in a subset of patients. The clinical and scientific rationale for single-shot trialing for pain management is lacking (1), and single-dose trialing may be used mainly to satisfy payer requirements. In general, trialing remains a controversial practice in IT therapy (1).

Patient Selection for Therapy Initiation—Safety

Safety concerns also prevent use of IT therapy for pain management, particularly because of their severity. Eight failure modes were scored in this category, and three had an RPN $>$ 75 (Fig. 2; Supporting Information Table S2). For example, worsening of an underlying disease at IT therapy initiation scored high on severity (S = 7.8) and moderate on frequency (P = 4.2). Underlying diseases and conditions include sleep apnea, peripheral edema, psychiatric conditions, hypogonadism, and renal insufficiency (1,9,10). Adverse events that may prevent IT drug titration (e.g., compromised respiration) received a high severity score (S = 7.5) and moderate frequency (P = 5.5), which produced an RPN $>$ 75. These failure modes are at particular risk of occurring in patients who are insufficiently monitored.

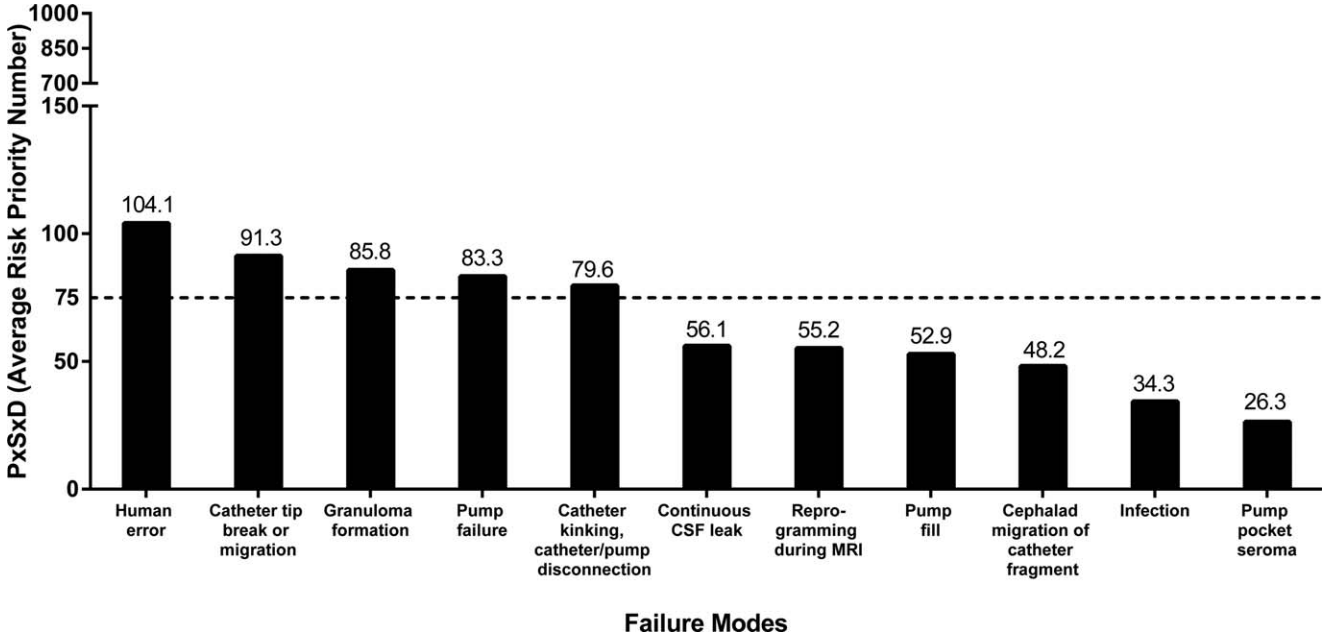

Figure 3. Patient safety during IT therapy. Abbreviations: CSF, cerebrospinal fluid; IT, intrathecal; MRI, magnetic resonance imaging; PxSxD, prevalence score multiplied by severity score multiplied by detectability score.

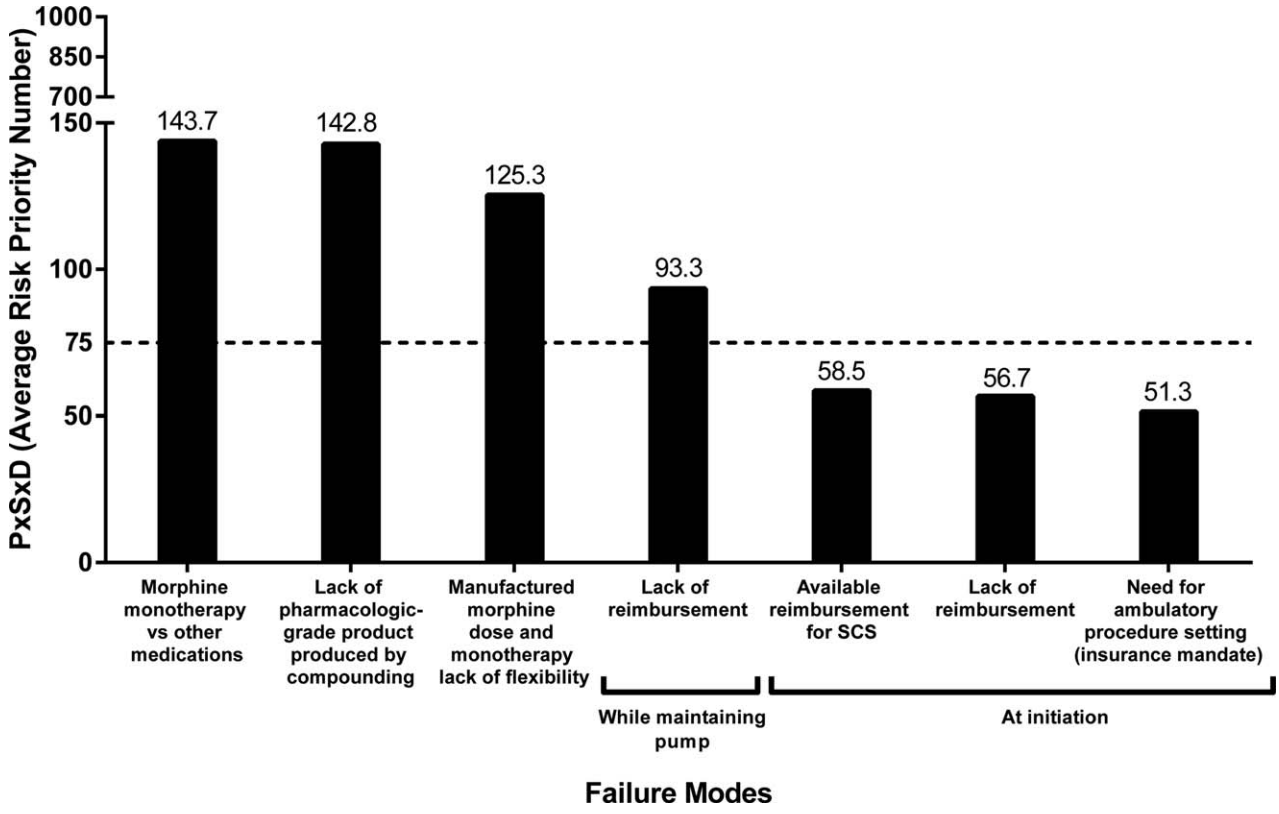

Figure 4. Product selection for intrathecal therapy. Abbreviations: PxSxD, prevalence score multiplied by severity score multiplied by detectability score; SCS, spinal cord stimulation.

The use of contraindicated medications (e.g., anticoagulants, antiplatelet medications) during initiation of IT therapy also showed a high severity score (S = 8.3), though the probability of encountering a patient on these medications was considered moderate (P = 4.2). Discussions explored whether and when IT therapy can be safely initiated in patients receiving anticoagulants or antiplatelet medications to reduce the risk of cerebrovascular or cardiovascular events from atrial fibrillation or other causes; the risk was considered a greater danger for noncancer pain patients and for those with stents. The group agreed on the importance of following guidelines from the American Society of Regional Anesthesia and Pain Medicine (ASRA) that recommend discontinuing antiplatelet and anticoagulant therapies for IT pump implantation (11,12).

Patient Safety During IT Therapy

The high severities of safety failure modes during IT therapy represent additional barriers to its use; of the 11 failure modes scored in this category, five achieved an RPN > 75 (Fig. 3; Supporting Information Table S3). The failure mode of human error (e.g., pocket fills, programming errors) leading to cardiovascular events, seizures, respiratory depression, and death was rated very high on severity (S = 9.2), moderate on detection (D = 3.9), and low on frequency (P = 2.9). Human errors were perceived as most likely to occur during initiation of therapy, dose titration, medication changes, and bridge boluses (to clear medication from the catheter during IT therapy transitions).

Granuloma formation during IT therapy scored high in severity (S = 7.8), moderate in detection difficulty (D = 5.0), and low in occurrence (P = 2.2). The incidence of granuloma may depend on the duration of IT therapy, type and concentration of medication, and rate of infusion (1,13,14). Intrathecal morphine has been the medication most associated with granuloma formulation (1,13). Most members of the panel agreed that the risk of undetected granuloma has remained stable and that a recent increase in reported cases may be attributable to wider use of IT therapy or better recognition of this potential AE.

The incidence of granuloma-associated paraplegia (caused by compression of the spinal cord [15]) appears to be waning because of greater awareness of this phenomenon with IT opioids and

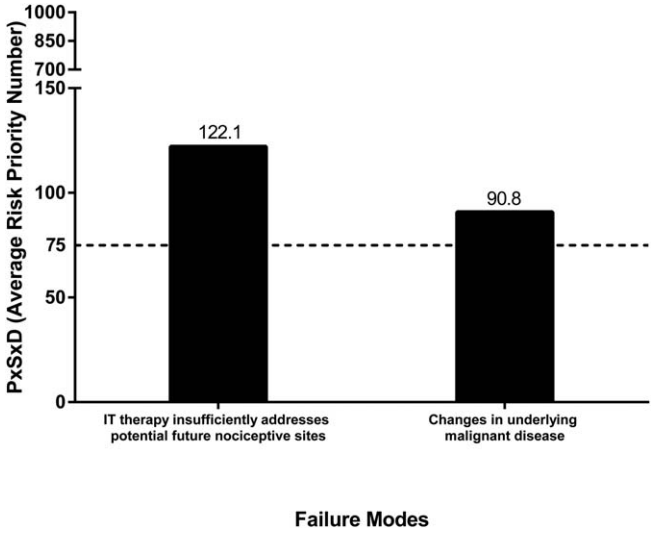

Figure 5. Cancer versus noncancer etiology of pain. Abbreviations: IT, intrathecal; PxSxD, prevalence score multiplied by severity score multiplied by detectability score.

methods for its prevention (e.g., decreased opioid dose and concentration [14]). However, diagnosis of granuloma before severe outcomes arise remains a challenge. The panel members varied in their use of magnetic resonance imaging (MRI) to diagnose granuloma on the basis of different clinical experiences. Some experts questioned the reliability of MRI, whereas others were concerned about the safety and efficacy of computed tomography (CT) with contrast dye to diagnose obstructive granuloma.

Catheter-related failure modes include kinking and disconnection as well as catheter tip breakage and migration at time of insertion. These issues were associated with RPNs > 75 because of the severity of the consequences ($S = 6.9–7.9$), which include loss of analgesia and onset of withdrawal symptoms. There is some evidence that older IT catheter models may be more likely to break and kink than newer models of catheters (16).

Pump failure also rated high in severity ($S = 8.9$), which led to an RPN > 75. It has been suggested that pump failure increases in frequency with longer use as well as with use of off-label products. This observation presents a potential conflict because many of the Polyanalgesic Consensus Conference 2012 recommendations include off-label medications (1).

Product Selection for IT Therapy

Access to and reimbursement for appropriate IT products is critical for successful therapy; of the seven failure modes scored under the category of product selection, four showed RPNs > 75 (Fig. 4; Supporting Information Table S4). Three failure modes evaluating manufactured monotherapy and compounded combination therapy achieved some of the highest RPNs among all categories studied (RPN = 125–144). The group preferred combination therapy to monotherapy in IT pain management because of potential efficacy and safety advantages, as supported by the Polyanalgesic Consensus Conference 2012 guidelines (1). Frequently administered combinations include opioids and bupivacaine and/or clonidine at various concentrations (1). The lack of manufactured IT combination products forces clinicians to obtain products from compounding pharmacies and accept the associated potential sterility and stability risks.

Reimbursement challenges for pump refills might also discourage IT therapy; this failure mode showed an RPN > 75 because of its high severity ($S = 7.0$) and moderate prevalence ($P = 4.3$). Lack of reimbursement might prevent patients from receiving their medication for pump refills. In addition, clinicians can often lose revenue because of limited insurance coverage for IT therapy, and many are not willing to accept a loss of income. Reimbursement challenges might be attributable to payers not being convinced of the long-term economic benefits of IT therapy.

RISK MITIGATION STRATEGIES

In addition to identification of obstacles for IT drug delivery, another goal of this analysis was to propose strategies to mitigate failure modes. Suggested plans to address the highly ranked failure modes included education, clinical research, and development of additional U.S. Food and Drug Administration (FDA)–approved IT products. These strategies may be considered by clinicians, institutions, pharmaceutical and device manufacturers, academic researchers, medical societies, and payers where appropriate.

Education and Training

The high severity assigned to the failure modes on delayed initiation of IT therapy, despite high doses of opioids or neuropathic pain medications, suggests that earlier IT treatment leads to better outcomes. Education of oncologists, neurologists, and primary care physicians on IT drug delivery by colleagues or pharmaceutical manufacturers may expedite referrals of qualified patients to pain specialists. Improving patient access to IT drug delivery may reduce protracted use of high-dose oral opioids or neuropathic pain medications and their associated AEs.

Institutions should train residents, fellows, and other medical staff on appropriate techniques for pump refills and programming to reduce the risk of human error. Medical societies representing individual specialties or multidisciplinary fields should consider creation of educational initiatives to increase cognitive and technical proficiencies regarding IT delivery. In addition, educating pain specialists on best practices for issues such as patient assessment and management (e.g., changing or discontinuing medications, surgical technique) may reduce the risk of treatment failure. Early granuloma detection (e.g., via MRI or CT) and preventive measures such as microdosing, bolus dosing instead of continuous infusion, and low opioid concentrations in IT pumps are also important educational topics. Clinicians should be trained to evaluate the frequency of unexplained IT pump stalls at every patient visit, which may indicate impending pump failure. Drug-related AEs may be managed by switching medications or adding adjuvant therapy (e.g., bupivacaine [17,18]).

Pharmaceutical and device manufacturers should assist pain specialists with designing patient-centric, safe, and effective treatment plans for IT therapy. Treatment must be individualized to the clinician's practice setting, to local resources, and to each patient. Characteristics of patients and their disease (e.g., cancer versus noncancer pain, active versus nonactive disease, degree and type of pain, ability to decrease oral opioids) are the most important criteria for decisions on IT therapy initiation.

Payers also require education from pharmaceutical manufacturers on the economic value of IT therapy because lack of reimbursement has been a major obstacle to its use. Payers are more convinced by data from pharmacoeconomic studies (such as two recent retrospective studies [19,20]) than by data from economic modeling. Economic benefits of IT delivery might be achieved by concomitant tapering and discontinuation of systemic medications (21). Until payers reliably reimburse for IT therapy, manufacturers should establish reimbursement programs for patients with limited insurance coverage to prevent disruption of their therapy and loss of revenue for clinicians.

Clinical Research and Tool Development

The lack of robust scientific and clinical evidence represents a major challenge for IT therapy use. Consensus is currently used more often than data to direct patient treatments (1). Researchers and pharmaceutical manufacturers could address this unmet need through controlled studies to validate best practices in IT therapy for pain management. Specifically, a placebo-controlled study to assess the ability of single-dose IT infusion trials to predict longer-term (six-month) success with IT therapy was proposed because the members of this advisory board were inconsistent in their use of single-dose trialing. A separate study is likely required for each IT drug because of differing pharmacokinetic properties (e.g., lipophilicity, which can affect distribution of a drug in the central nervous system [1]). Additional trials should be performed for each route of administration (e.g., IT, epidural) because of differences in drug

dispersion. Although stability studies for IT drugs have been published (22,23), trials on compatibility between drug and pump are limited (24), particularly for off-label and combination drug use. Compatibility studies may help to identify and minimize the risk of pump failure. To decrease the potential for human error, the members of this advisory board requested new pump and catheter technologies from device manufacturers.

There is also a need for a validated quality of life scale that includes functional assessments (beyond the customary evaluation of symptomatic pain relief) and is designed to be used in conjunction with IT therapy. In the absence of such a tool, efficacy of IT therapy is measured by individualized patient goals that may be specific to the underlying disease. Because functional goals vary across diseases that cause intractable pain, developing a scale that includes function may be a substantial undertaking for researchers.

Clinical Development

The literature suggests that IT therapy can be effective for neuropathic pain (25). However, nonopioid neuropathic pain medications such as gabapentin and clonidine are not currently FDA approved for IT administration. Their addition to the armamentarium of IT medications would likely increase adoption of IT therapy and potentially improve the management of neuropathic pain (e.g., from diabetic neuropathy, postherpetic neuralgia, or complex regional pain syndrome). The IT treatment of peripheral neuropathic pain represents an opportunity for further research by pharmaceutical and device manufacturers and clinicians.

Use of combination IT drugs is common practice among pain specialists, but FDA-approved manufactured combination products are not currently available. Therefore, clinicians must rely on nonstandardized products from compounding pharmacies. Recent legislation has increased the scrutiny of compounding pharmacies, which may lead to improvement in the safety of compounded products (26). To further ensure that combination IT products are safe, the development of manufactured IT combination products including clonidine and bupivacaine together or each with an opioid was suggested.

DISCUSSION

Intrathecal infusions are associated with numerous risks because of the complex interplay among drug, device, clinician expertise, and patient status. Practitioners administering IT therapy consider the likelihood of different types of failures and decide on the acceptable risk for each patient. There is an unmet need for a more formal approach to the assessment of risk. The novel application of FMEA to an IT advisory board allowed for a systematic approach to risk-tolerance assessment.

The FMEA process was performed by a panel with experience in IT therapy; approximately 50% of the advisory board participants have contributed to consensus guidelines. In contrast to best practice/consensus guidelines for IT therapy, this study focused on the barriers to adoption and evaluated the clinician's risk tolerance in overcoming these obstacles. Barriers to use of IT therapy include the potential to harm the patient, and many of these safety concerns have also been described in best practice and consensus guidelines. However, FMEAs and best practice/consensus guidelines serve different purposes; best practice/consensus guidelines drive consensus among experts on which method has the highest likelihood of success (i.e., for efficacy and safety), whereas FMEA analyzes the risks themselves. After the FMEA analysis, questions regarding acceptable versus unacceptable risk are evaluated systematically. For risks considered unacceptable on the basis of frequency, ability to detect, or severity of outcome, specific actions are identified to reduce or control the risk. Mitigating risk lowers barriers to IT therapy adoption and improves patient access. The results from FMEA can be used to complement strategies in best practice/consensus guidelines.

Of the 37 failure modes in the analysis, 17 (46%) had an RPN $>$ 75. The FMEA process did not reveal priorities contrary to current guidelines, but it did highlight variability in risk tolerance among practitioners for procedures with vague guideline recommendations (e.g., single-dose trialing). Focusing on minimizing risks from the highest-ranking failure modes would theoretically produce the greatest clinical impact; therefore, risk management strategies were generated for the top 17 failure modes. Addressing failure modes regarding patient and product selection was considered critical.

A key benefit of the FMEA methodology is the collection of input from multiple experienced clinicians with different perspectives on each issue. Efforts to include participants with a range of practice settings and specialties, varied familiarity with IT therapy, and differing risk tolerance produced a wide distribution of scores and facilitated development of risk mitigation strategies that are applicable to most practitioners administering IT therapy. Additional benefits of FMEA include its quick implementation (e.g., in a one-day meeting), the lack of complex statistical analyses required, and its usefulness in developing high-priority tactics to minimize risk.

As a limitation of the FMEA process, not all medical concerns are easily translatable to failure modes. Patient selection based on cancer versus noncancer pain did not lead to a robust risk mitigation discussion, though both failure modes in this category received an RPN $>$ 75 (Fig. 5; Supporting Information Table S5). Etiology of pain is a clinical concern and may play a role in patient selection, but it is not a preventable risk that is well suited as a failure mode for FMEA. The panel proposed that separate FMEAs, one for cancer pain and another for noncancer pain, would be optimal for examining the risks of IT therapy in these conditions.

Additional limitations of the FMEA process include the small sample size, which is a concern with any expert panel and may lead to selection bias. Although an FMEA for an engineering process may be conducted with six participants (3), the optimal sample size for an FMEA applied to IT therapy is unclear. The method of isolating and analyzing each failure mode may seem limiting in a multifactorial decision-making process such as that for IT therapy, but multiple failure modes can sometimes be addressed by a single action item (e.g., training, development of a novel formulation).

The FMEA process produced several suggested research and educational initiatives to address failure modes. The proposed strategic plan to increase adoption of IT therapy requires effort, resources, and time. Some components of the plan (e.g., sharing best practices) can be executed more quickly than others (e.g., clinical trials). The goal of continual improvement drives FMEA, and the process should be revisited to test the merits of the methodology and the effectiveness of its recommendations.

CONCLUSION

Ensuring therapeutic success in a complex medical environment such as IT drug management requires understanding and prioritization of the associated risks. Failure modes and effects analysis may be an efficient method of prioritizing risks and evaluating their consequences. The FMEA methodology assisted in identifying key challenges of IT therapy and helped build a consensus on methods to

overcome barriers to safe and effective treatment. The methodology identified appropriate patient selection as the most critical component for successful management of pain with IT therapy; efforts to address failure modes related to patient selection will likely have the greatest clinical impact. Human error, catheter issues, pump failure, and granuloma formation were considered severe safety concerns during IT therapy. In addition, combination therapy was the preferred approach to managing pain using IT therapy, but its use is limited by institutional restrictions on reimbursement and stability/compatibility issues with pumps.

Proposed mitigation strategies included education, training, research, and new product development opportunities that may be pursued by clinicians, institutions, pharmaceutical and device manufacturers, academic researchers, medical societies, and payers. The FMEA process may prove to be a useful tool in medicine to balance risks and benefits, improve clinical outcomes, reduce costs and liability, and identify opportunities for further research.

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Drs. Saulino and Fisher participated in the meeting from which data were collected, and Dr. Saulino had a supervisory role for the manuscript. All authors were involved in the concept and design of the manuscript, provided crucial revisions for important intellectual content, and approved the final content.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

COMMENTS

Having participated in multiple FMEAs in the medical device industry – including analyses of intrathecal drug delivery (IT-DD) pumps, catheters, procedures, and drug therapies – this reviewer was intrigued by the title of the article: The Application of Failure Modes and Effects Analysis (FMEA) Methodology to Intrathecal Drug Delivery for Pain Management (1). As summarized in the article and other references, "Failure mode

and effects analysis (FMEA) was . . . developed by reliability engineers in the late 1950s to study problems that might arise from malfunctions of military systems. . . . It involves reviewing as many components, assemblies, and subsystems as possible to identify failure modes, and their causes and effects. For each component, the failure modes and their resulting effects on the rest of the system are recorded... . . . An FMEA is used to structure Mitigation for Risk reduction based on either failure (mode) effect severity reduction or based on lowering the probability of failure or both (2). FMEA methods also can apply to studies of how people fail to use devices properly, and even to how physicians order unnecessary diagnostic tests or mis-prescribe medications. The application of FMEA-like methods to healthcare facility and medical practice evaluations, albeit less well grounded than other applications, is already a fact of life for hospital administrators. In any setting, in order to make sense, and in order to be valid, an FMEA requires unambiguous well-defined inputs and endpoints based on the laws of nature (i.e. physics and chemistry), and in the case of medical practice, based on physiology and clinical data with a high level of evidentiary value.

One example of an intrathecal drug delivery (IT-DD) product and process-related FMEA was the effort to minimize the occurrence of IT drug overdoses from unintentional injection of medication into a catheter access port instead of into an IT-DD pump reservoir (3). The device components, assemblies, subsystems, accessories, physician actions, and failure modes that were identified and modified (in some cases, more than once) included the design and construction of the side- and refill ports, the size of the needles in refill and access kits, the design and labeling of templates to guide needle insertions, the instructions for use, and even the colors of packaging for kits with different functions. The process, although it was straightforward, and is summarized in only a few sentences, took months of work by teams of engineers – including empirical (hands-on) testing of proposed device and accessory modifications. Other historical FMEA-like exercises (not necessarily formal FMEAs) have involved nationwide efforts to improve specific medical practices in the absence of any changes to existing drugs or devices. A particularly salient example was the effort to reduce failures of emergency room (ER) personnel to administer aspirin to patients suffering from a suspected acute myocardial infarction (MI). Before this FMEA-like effort, although the potentially lifesaving benefits of early aspirin administration in MI were well established, this cheap and easy treatment was used in fewer than half of patients (4). In that case, points of intervention that were analyzed included 911 operators, first responders in the field, ER and hospital physicians, nurses, pharmacists, medical trainees, and the general public. Although the aspirin example was not a formal FMEA, comparable methodology was used to identify correctable failure modes and opportunities in both examples – whether related to a device, or limited to human actions. The failure endpoints (wrong port injection, failure to administer aspirin) were obvious, undesirable, traceable in contemporaneous records, and amenable to correction. Finally, the elimination of unintentional pump refill drug overdoses or imperfect care of suspected MI patients led to improvements in patient survival and public health.

When one compares such examples with this publication – perhaps inaccurately called an FMEA – the latter falls short in terms of subject matter (endpoints selected for analysis), depth of analysis, methodology, and results. The introduction points out that "The potential for serious adverse events (AEs) must be weighed against the analgesic benefits of IT drug delivery . . ." (1). Readers should be mindful that some 30 years after US-FDA approval of implantable IT-DD micro-infusion pumps to deliver preservative-free morphine sulfate to treat chronic pain – without clinical trials, and regardless of etiology – no genuine evidence exists to support the notion that IT-DD effectively treats any chronic non-cancer pain disorders, the most common indications treated with IT therapy. References cited by the authors to support efficacy claims consist largely of industry-sponsored aggregations case reports, meeting proceedings, single institution series, and other low level evidentiary sources. In contrast, well documented research has revealed that the risk of premature mortality associated with IT-DD in the non-cancer pain population is staggeringly high – both immediately after implant (1 per 1,000 implants) and especially during the first year of follow-up (40 per 1,000 implants, or 3.9% as cited in this article) (1,5). For comparison, the 3.9 percent death rate associated with IT-DD exceeds the one-year mortality after complex spinal surgery (including instrumentation and fusion) in the Medicare population (6). Safety-related practice guidelines cited by the authors appear to represent an industry-sponsored defense of IT-DD therapy. Readers should remain cautious because such publications may provide insufficient guidance to assure patient safety. If IT-DD has unproven efficacy, but is particularly lethal in the non-cancer pain population to whom it is most commonly administered, what was the object of the exercise described in this paper?

Critical reading provides some clues. In the analyses of patient selection and efficacy the authors define failure as a delayed decision, or a decision not to implant an IT-DD system. Such failures are attributed to patient referral patterns (owing to gaps in referring physicians' knowledge, or physician safety concerns) or to the putatively unreliable effects of single-shot drug trials. Such high priority failure modes do not address analgesic efficacy at all – but rather, the failure of therapy marketing when a candidate patient is not implanted. The analyses of patient selection and safety are similar. They deal with potential barriers to implantation or candidacy for therapy – namely, marketing barriers, not actual patient safety. The analyses of patient safety during IT therapy also are incomplete. The authors consider systemic overdosage from pocket fills, massive IT overdosage from catheter access port injections, complications associated with drug concentration changes and bridge boluses, with death from a variety of device-related root causes all together under the heading of human errors – meaning errors committed by physicians or their ancillary staff. In reality, individuals in the medical device industry committed the errors in device instructions and labeling that contributed to patient deaths from IT drug overdosage after priming boluses (and possibly, after bridge boluses).

The list of adverse events selected for consideration also is incomplete, and recommendations put forward to overcome barriers to therapy acceptance at times conflict with safety considerations. The selective inclusion of some failure modes, omission of others, and the presence of internal contradictions in this publication are features that genuine FMEA exercises strive to avoid. On one hand, the authors endorse the administration of unlabeled or compounded drugs in discussions of efficacy, yet raise concerns about off-label or compounded drugs causing pumps to malfunction, which is a safety-related failure. A minor point that the authors may not have known about is that approved, manufactured, on-label drugs also can cause internal pump corrosion and stoppage. However, a different category of neurological AEs that the authors did not to address is always associated with the use of off-label or compounded IT drugs or admixtures – namely, partial or complete paralysis owing to direct toxicity of such drugs or admixtures on the spinal cord (7).

Turning to methodology, the authors arrived at the average risk priority numbers by, of all methods . . . a vote. This assumes that numbers which arose from the collective memories of their individual experiences represent real-life events. If that were the case, the errors, omissions of some factors, and the selective inclusion of others would not have been identified in the preceding paragraphs. Published research and public information are available regarding the incidence rates for pump stoppage, catheter complications, device infections, and even death (5, 8, 9, 10). The authors could have looked those kinds of things up instead of

relying upon memory, clinical impressions, voting and/or averaging to arrive at probability estimates. Then there is a further matter of definitions and numerical incidence categories. An recognized set of definitions in the pharmaceutical and medical device industries, and among international regulatory bodies, has established the categories and boundaries to describe the incidence of adverse events (11). It consists of five non-overlapping categories – not the ten, collapsed into six, used by the authors. Each category is associated with a specific incidence range from < 1/10,000 (very rare) to > 10/100 (very common). An implant-related mortality rate of 1/1,000 makes that an uncommon or infrequent adverse event, whereas a one-year mortality rate of approximately 40/1,000 (3.9%) is, by definition, a frequent or common adverse event.

The aggregate effect of the errors and biases in this publication means that readers who accept this article at face value are at risk for being seriously misinformed about the real risks and potential failure modes associated with IT-DD therapy for pain. It bears repetition that the highest priority failures addressed by this article are delayed implantation or non-implantation of IT-DD devices for chronic pain. Such decisions – made more often and by more physicians than decisions or recommendations to perform an implant – likely have saved the lives of thousands of patients who otherwise might have been exposed to an often ineffective, invasive, costly, and potentially lethal therapy. In contrast to the position taken by the authors, physician decisions not to implant a chronic pain patient or not to refer a patient for implantation of an IT-DD device puts them on the side of historical progress. It is past time to recognize that over the past three decades, the increased use of opioid medications to treat chronic non-cancer pain has been a grievous error for which the medical profession bears considerable responsibility. Changes in practice and prescribing habits are inevitable, and hopefully will not require generations to complete.

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This is the first described use of FMEA to assess risk and its mitigation in intrathecal infusion therapy for analgesia. Complementing the Polyanalgesic Consensus Conference Guidelines, this review article addresses the methodology of FMEA and its application to a complex pain therapy. I applaud the authors and participants in the paper for sharing their experience and expertise and thoughtful considerations for quality improvement in a novel way, which will be useful not only in intrathecal therapy, but also in other complicated, high risk medical interventions.

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Comments not included in the Early View version of this paper.

