CASE STUDY

Locally invasive and metastatic endometrial cancer: Multiple issues functioning in a multidirectional manner

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ABSTRACT

A 32-year-old woman with locally invasive and metastatic endometrial cancer was admitted to the hospital for the treatment of crescendo pain. The effectiveness of her medical and psychosocial care was mitigated by four issues: (1) the intractable nature of her pain, (2) substance abuse, (3) mental illness, and (4) interorganizational conflict. This case report is both a chronicle and review of the literature of these multiple issues that converged together to adversely effect the patient's overall care.

Key words: crescendo pain, substance abuse, communication

INTRODUCTION

This case study describes the dynamics of four concurrently operating and overlapping issues simultaneously functioning in a multidirectional manner and how they influenced a young woman with cancer pain, her family, and her three independently functioning treatment teams. These issues are as follows: (1) crescendo pain management in a young dying patient with rapidly progressive neuropathic, bone, and visceral pain; (2) a past and present history of substance abuse; (3) comorbid preexisting psychiatric illness; and (4) suffering in the context of dysfunctional professional interorganizational dynamics.

CASE HISTORY

A 32-year-old Manhattan film maker presented to her physician complaining of sharp, persistent right groin and generalized colicky pelvic pain associated with a 3-month history of heavy menstrual flow. A Papanicolaou test revealed atypical endocervical glandular cells. A transvaginal ultrasound of the pelvis revealed a large complex right adnexal mass and numerous other circumscribed masses adjacent to both ovaries and iliac vessels bilaterally. Dilatation and curettage demonstrated high-grade invasive undifferentiated cancer of the endometrium. Abdominal and pelvic computerized axial tomography (CAT) scans with contrast revealed large lytic masses as well as pathological fractures at the pubis symphysis and inferior pubic rami bilaterally and at the left acetabulum and right iliac bones. Fine needle aspiration biopsy of her right iliac bone revealed metastatic highly undifferentiated carcinoma (stage IV B). Total body blood pool/bone imaging studies revealed increased uptake in the right sacroiliacjoint, bilateral pubic rami, left acetabula, and right iliac bones. A marijuana, hashish, heroine, and cocaine user for many years, she reportedly had been neither hospitalized nor been in rehabilitation. Her pain, initially managed with Percocet 5/325 mg q4h, Duragesic 25 mg q72h, and Motrin 600 mg q6h resulted in unsatisfactory pain relief. She was given progestin therapy and pelvic external beam radiation.

The anesthesiology based pain service consultants visited the patient at her apartment in the company of her family. She appeared to be fearful, sleepless, confused, and disoriented and in pain and was unable to sit or lie comfortably in any position. Her pain medications were promptly adjusted. She was identified as an eventual candidate for an intrathecal analgesia pump. Accordingly, both a psychiatric consultation and a pain clinic appointment were scheduled. Urine toxicologies were discussed but not pursued. The consulting psychiatrist diagnosed a longstanding borderline personality disorder yet approved an anticipated intrathecal pump implantation. Several weeks later at her first clinic appointment, the patient complained of progressive right groin and bilateral hip pain. The patient perceived that the crescendo pain she was experiencing represented healing. She was told, however, by an attending physician that the pain was more likely due to disease progression. Subsequently, her reports of uncontrolled pain and analgesic requirements rose significantly (Appendices 1-4). Excellent pain control was achieved with oral methadone. She was begun on a comprehensive bowel regimen and

was followed at home. During the subsequent weeks, the patient slept well and enjoyed her life, editing her film projects, dying her hair several different colors, and spending time with her fiancé, family, and friends.

Subsequent constipation became an overriding physical and emotional preoccupation requiring hospitalization. In the hospital, her constipation was successfully treated with lactulose and soap suds enemas. The patient was discharged home. Within 1 week, severe constipation and crescendo pain required rehospitalization. Oral opioid were not rotated for differential effects on her constipation or crescendo pain. Rather, anticipating continuously and rapidly escalating opioid requirements and recurrent constipation, an intrathecal trial of morphine and adjuvant medications were suggested. If significant pain relief without constipation was achieved, an implanted intrathecal opioid pump was recommended. Tearfully, the patient explained that this course of action validated her fears that she would die with cancer and in pain. She was despondent over the idea that the opioid pump would survive her and was distraught that the surgery would further desecrate her body. Her pain medication requirements rose. At a rapidly convened family meeting, her pain physician stated that, given her recurrent constipation and rapidly escalating analgesic requirements, intrathecal pump analgesia therapy represented the best risk/benefit profile. After much reconsideration, the patient accepted the pain management plan. A temporary intrathecal catheter was placed under fluroscopy in a radiology special procedure room. A 2-day intrathecal trial of morphine succeeded in successfully relieving her pain without constipation. In the operating room the following day, a Medtronic 18-cc intrathecal pump was surgically implanted in her left flank and a 3-mg morphine loading dose was provided. Postoperatively, the patient complained bitterly of surgical pain despite supplemental IV bolus and PCA morphine. Intrathecal fentanyl and bupivacaine were added to the pump infusate, resulting in significantly improved postoperative analgesia. A repeat bone scan and pelvic magnetic resonance imaging demonstrated widespread pelvic disease progression to bone and right lumbar nerves 2-5. Pelvic pain reports escalated. Clonidine was added as a neuropathic pain adjuvant. Intrathecal morphine and clonidine dosages were quickly doubled, with no appreciative improvement in analgesia. She was hospitalized for aggressive pain control.

During the next several weeks, though intrathecal morphine dosages were increased to an anecdotal ceiling limit of 25 mg/24 h, no improvement in analgesia was noted. Intrathecal morphine was rotated to intrathecal Dilaudid in progressively increasing dosages resulting in persistently unreliable analgesia. Despite exponential increases in oral, IV, and intrathecal opioid and adjuvant pain medications, her mental status remained remarkably oriented, alert, and conversant. Her oncologists and palliative medicine physicians were frustrated and dissatisfied with her pain management care and expressed their views to her family. Her oncologist wrote in the patient's chart: "The patient is in excruciating pain and is clearly far worse off now than when she was first admitted for pain management." Another oncologist wrote: "The patient is clearly and obviously undermedicated and, in addition to her intrathecal medications, requires larger and more frequent continuous intravenous opioid boluses." A crisis of confidence ensued amongst the patient, her family, and the pain, oncology, and palliative care services. Triangulation of individual relationships developed, with secret and separate understandings established. Contradictory information and misunderstandings resulted in bad feelings and disrupted trust. In response, the family rarely left the patient unattended. Family initiated discussions of discharge and home care ensued. The patient complained of sharp, intermittent left pelvic pain. A new pelvic CAT scan revealed an extrinsically obstructed left ureter. In cystoscopy, the ureter was stented. The patient tolerated the procedure poorly, requiring 35-mg IV Dilaudid to lie quietly supine for the required 20-minute interval. In the recovery room, with the family present, the urologist reportedly exclaimed "What the hell are they doing to that girl? I am appalled that they cannot control her pain." An intrathecal pump function dye study under fluroscopy demonstrated excellent pump function. Afferent and efferent tubings were clearly patent and intact. No evidence of intrathecal granulomas were found at that time or several hours later on a follow-up CAT myelogram. There were discussions with the patient and her family concerning the utility and placement of a lumbar retrograde epidural catheter for the purpose of directly infusing local anesthetics on the involved lumbar nerves. Additionally, neurosurgical solutions such as percutaneous cordotomy or a midline myelotomy were discussed. However, as the patient remained remarkably coherent and ambulatory at the time of these discussions, she and her family were reluctant to consider either suggestion. Several days later, when the patient and family reconsidered and wished to pursue all pain management options, the patient was coagulopathic.

External radiation therapy to both hips and to the right iliac crest was resumed. The patient's pain continued to accelerate despite intrathecal opioid rotation to methadone. Supplemental intravenous methadone and intravenous ketamine infusions were begun, which resulted in seemingly improved analgesia. Subsequently, several family members were observed increasing the automated infusion rate while the patient slept presumably in response to perceived patient discomfort and/or pain. When this issue was discussed with those involved, denial, outrage, and animosity were expressed. Do-not-resuscitate orders were written and signed and hospice was discussed. Following an in-hospital hospice evaluation, the

patient was transferred to a nearby university inpatient hospice facility. There, the treatment team "unfamiliar and uncomfortable" with her analgesic therapy reportedly "significantly curtailed" all parenteral and intrathecal medications. No further contact with the family occurred despite repeated inquiries. One of her physicians had seen her obituary in the newspapers the following week. We do not know whether or not the reported changes in her multiple route opioid dosages resulted in more or less pain and suffering.

DISCUSSION

The patient described in this case report suffered from intractable pain. The pattern of rapid escalation in the intensity of pain and anguish due to disease progression in terminal illness is well known. The American Alliance of Cancer Pain Initiatives Statement on Intractable Pain Treatment defines it as a state in which "the cause of the pain cannot be removed or otherwise treated in the course of general medical practice and no significant, or sustained, relief of pain is possible or has been found after reasonable efforts."[1] Multiroute optical and adjuvant medication dosage escalation, interventional neural axial blockade, and surgical procedures describe the modern response to intractable pain and suffering. Our patient received oral, transdermal, transmucosal, parenteral, and intrathecal opioids and adjuvant medications in what we considered to be measured, reasonable though often dramatic responses to her crescendo somatic, visceral, and neuropathic pain. We acted under the primary therapeutic and ethical principle of individualizing opioid medication dosages to the best possible outcomes at any given moment in time without regard, if required, to gestalt or conventional dosing schedules.

Pain, comorbid psychiatric conditions, and substance abuse are not infrequently simultaneously encountered. We perceived that the patient's suffering was intensified by her borderline personality disorder, resulting in wide mood swings and histrionic behavior. Both her normal and clinical grief reactions were adversely affected by her ineffective coping skills and brinkmanship. Conceivably, single or multiple drug withdrawal and/or a sustained lack of reward response during and associated with her prolonged hospitalization may have further complicated her ability to cope with her pain and grief. The patient's treatment team consisting of the anesthesiology based pain medicine service and the internal medicine-based palliative care medicine and oncology services had the prerequisite professional knowledge to meet the patient's complex needs. Whether they were met effectively requires examination of the following issues: (1) What were the reasons for the patient's apparent lack of satisfactory and sustained analgesia despite ever-increasing quantities of rotating opioid and adjuvants delivered independently and then simultaneously by multiple routes? (2) Were her substance abuse and psychiatric history contributory to her pain and suffering? If so, how? (3) To what degree did the professional staff's interorganizational psychodynamic relieve and/or aggravate the pain and suffering of the patient and her family?

Tolerance, a pharmacological property defined by the decreased responsiveness to the pharmacological effects of a drug resulting from previous exposure or the need for increasing dosage to maintain an effect, does not usually appear to be responsible for unexpected opioid dose escalation requirements.[2] Tolerance demonstrates selectivity so that the tolerance to one opioid is not necessarily accompanied by tolerance to others. Mechanisms such as down-regulating or decoupling of drug receptors have been suggested as explanations for tolerance. Animal models demonstrate the instance of multiple μ-opioid peptides. Morphine sulfate, methadone, fentanyl, M6G, and heroine have experimentally verified separate and distinct receptor peptides with which they couple in highly selective affmity.[3] The practice of rotating opioids for pain management is based on the concept of μ-opioid peptides subset selectivity and incomplete cross tolerance. Its utility is found, for example, in morphine-induced neuroexcitation, where increased pain, hyperalgesia, and allodynia, as well as myoclonus and seizures, occasionally occur in patients receiving high levels of oral or intravenous morphine (though uncommonly reported with intrathecal morphine).[4] Increased serum and cerebrospinal fluid levels of M3G have been associated with these phenomena in contrast to increased levels of M6G that are associated with the spectrum of classically related morphine side effects.[5] Opioid-induced pain has rarely been reported with opioids other than morphine. Opioid rotation to a structurally dissimilar opioid, ie, fentanyl or methadone, allows for the clearance of active morphine metabolites from the patient while effecting analgesia through structurally dissimilar receptors is a safe and effective intervention.[6] The role of N-methyl-D-aspartate (NMDA) receptors in mediating opioid-induced pain by stimulating windup phenomena is suggested by the utility of methadone and its NMDA antagonist effects in relieving hyperpathia, allodynia, and other forms of neuropathic pain. Opioids (morphine in particular) also influence locomotor activity in some cerebral nuclei via sigma (nonopioid) receptors that facilitate confusion. Serotonergic syndromes have been reported in susceptible opioid-treated patients, resulting in hypertension, facial flushing, tachycardia, diaphoresis, chest pain, agitation, confusion, psychosis, respiratory depression, and coma. Naloxone in these cases reversed the symptoms in only 50 percent of the patients.[7]

Comorbid substance abuse often complicates the experiential/emotional content and the expression of pain. The principles of pain treatment in the addicted patient have been well described by Savage et al.[8] Individuals with addiction disorders are at special risk for

suffering because of inadequate pain management. Patients and their physicians often have difficulty distinguishing which aspect of their pain represents somatic, visceral, and/or neuropathic pathology as a result of their underlying disease state versus that which represents cravings and/or withdrawal independent of disease pain. How is chronic opioid use and addiction related to pain tolerance and analgesia? Opioid analgesia and reward physiologies can and do overlap at the μ-opioid receptor.[9] Certain midbrain structures (ventral and dorsal segmental areas) when stimulated produce both naloxone-sensitive reward and profound analgesia. In vivo examples of overlap between opioid addiction and pain systems include the hyperalgesia induced in pain-free morphine-tolerant animals and the hyperalgesia that accompanies withdrawal in opioid addicts.[10] Preexisting differences or adaptations in systems related to opioid addiction are demonstrated not only in how nociceptive stimuli are perceived but also in the relative efficacy of analgesic agents in providing pain relief. Martin and Englis[11] found that nondrug addict controlled subjects tolerated cold oppressor pain over five times as long as those classified as drug addicts. Ho and Dole[12] reported that cold pressor pain thresholds for drug-free methadone patients were significantly less than those of their nonaddict siblings, suggesting preexisting or lasting changes in their pain responses to chronic opioid use. Compton et al., [13] studying current and former opioid abusers who were all on methadone maintenance, found that active opioid users tolerated cold emersion approximately one-half as long as ex-opioid and ex-cocaine abusers. Repeated intermittent morphine dosing resulting in analgesic tolerance has been demonstrated to induce NMDA hyperalgesia in pain free mice.[14] These studies suggest that chronic opioid use and/or methadone maintenance may induce pain and/or make individuals less tolerant of pain. Alternatively, opioid addicts may be inherently pain intolerant. Drug-induced adaptations in the transcriptions of specific genes are described as an important mediators of drug addiction and often parallel those associated with pain tolerance, wind-up phenomena, and hyperalgesia.[15] Adaptations and altered gene expressions initiated by acute and chronic exposure to opioids and cocaine and which are common to opioid and dopaminergic brain receptors include CFOS, acute and chronic FOS transcription factors, CREB (cyclic AMP response element binding protein), phospholipase A2, and G Protein/receptor phosphorylation.[16] In one study where inbred strains of mice were known to differ with respect to μ-opioid binding activity, the pain intolerant strains were also those that found opioids the most reinforcing and developed significant opioid tolerance to acute and chronic dosing.[17] The genetic locus underlying this patterned response is identified as the OPRM μ-opioid receptor, polymorphisms of which have been reported in the DNA of human opioid addicts. The phenotypic expression of this genetically generated opioid response is characterized by an inverse relationship between pain tolerance and opioid reinforcement.[16] Opioid addicts and patients receiving chronic opioid medication, therefore, may require more opioids than do other patients to obtain pain relief from acute and/or chronic pain because of induced or preexisting genetic pain intolerance.[18] Pain interventions may indeed need to be very aggressive to provide adequate analgesia for former or current opioid and possibly cocaine addicts.

How does one differentiate and evaluate active premorbid behavioral disorders from normal anxiety and grief behaviors resulting from living a life terminating illness?[19] Psychiatric evaluation had established that this patient had a longstanding cognitive and affective disorder resulting in stormy relationships and self-defeating behavior. Intense feelings of devaluation/dependency, entitlement/demandedness, and abandonment/annihilation limited her range of emotional response to the present situation. Additionally, the patient answered affirmatively to the question "Do you feel depressed?" citing feelings of guilt, shame, hopelessness, and unworthiness. Specifically, her emotional suffering on at least eight different occasions seemed to significantly have increased both her pain perceptions and analgesic requirements (Appendices 1-4). These events were as follows: (1) Alteration in her belief that the increasing pain she was experiencing might not represent healing but rather progressive disease. (2) Her hospitalizations for constipation. (3) The initial recommendation of an intrathecal pump. (4) Postoperative pain. (5) Hospitalization for crescendo pain. (6) Interorganizational dysfunction-multiple examples. (7) Discussion of home care or home hospice care. (8) Discussion of hospital discharge to hospice.

Physicians are unfortunately notoriously challenged when it comes to communicating with each other. Many guidelines for interspecialty communication have been offered.[20] Common key principles describe the value of both task oriented communication and setting clearly defined areas of responsibility. When physicians in different specialties communicate, we might do well to ask ourselves: "What is my colleague's understanding of this situation that seems so perfectly clear to me?" When communicating with another physician about a mutual patient, a report check list has been reported of proven value: (1) Am I addressing the right person? (2) What do I know about this patient that the other person should know, and/or do I want to know from the other person? (3) What does this mean for the patient's future care? (4) Who is going to do what? Who is now "the doctor" for this patient? (5) How do we communicate again if things are not going well? Angry verbal exclamations, written insults, and imperatives assign shame, guilt, and blame. Personality issues, promotional leadership, and private

agendas can and do sabotage professional role recognition and shared decision making. Some degree of conflict seems inevitable reflecting as it does the attitudes learned from our instructors in our formal medical training and our tacit agreements to believe them (Appendix 5).

SUMMARY

The treatment of patients with intractable crescendo cancer pain, substance abuse, and comorbid preexisting psychiatric disorders is challenging because each entity has a relationship with opioid pain modulation and reward reinforcement systems that subsequently impact on pain tolerance and/or analgesia. The International Association for the Study of Pain definition of pain presupposes the likelihood of increased pain and suffering when a patient's emotional needs are overlooked and/or unmet. Substance use as well as certain preexisting/comorbid psychiatric issues also, in all likelihood, predispose the patient to low pain thresholds and tolerances as well as low analgesic sensitivities. Concomitant dysfunctional interorganizational dynamics complicated and amplified the patient's, family's, and healthcare teams' frustrations and suffering. Misunderstandings concerning applied basic science (eg, equianalgesic dosing of medications given in by multiple routes), misrepresentations, and mistrust of each other's motives and intents contributed to the frustration over the patient's refractoriness to innovative pain relief therapies and reframed the patient's in-hospital experience with superimposed turmoil. Communication, respect, empathy, compassion, active listening, and the willingness to see things differently (to perceive the obvious in a different light) are essential attitudes for effective use of the many available resources brought to bear by interdisciplinary team efforts.

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Appendix 1

CHARGED EMOTIONAL EXPERIENCES CAUSING INCREASED ANALGESIC MEDICATION REQUIREMENTS

1. Alteration in the patient's belief that her increasing pain might not represent healing but rather progressive disease.
2. Hospitalization for constipation/setback.
3. Recommendation of an intrathecal pump.
4. Intrathecal pump implantation and postoperative pain.
5. Hospitalization for crescendo pain.
6. Interorganizational dysfunction, multiple examples.
7. Discussion with family members regarding unauthorized adjustment of patient dose medications.
8. Discussion to discharge patient to home care with do-not-resuscitate orders.

Appendix 2

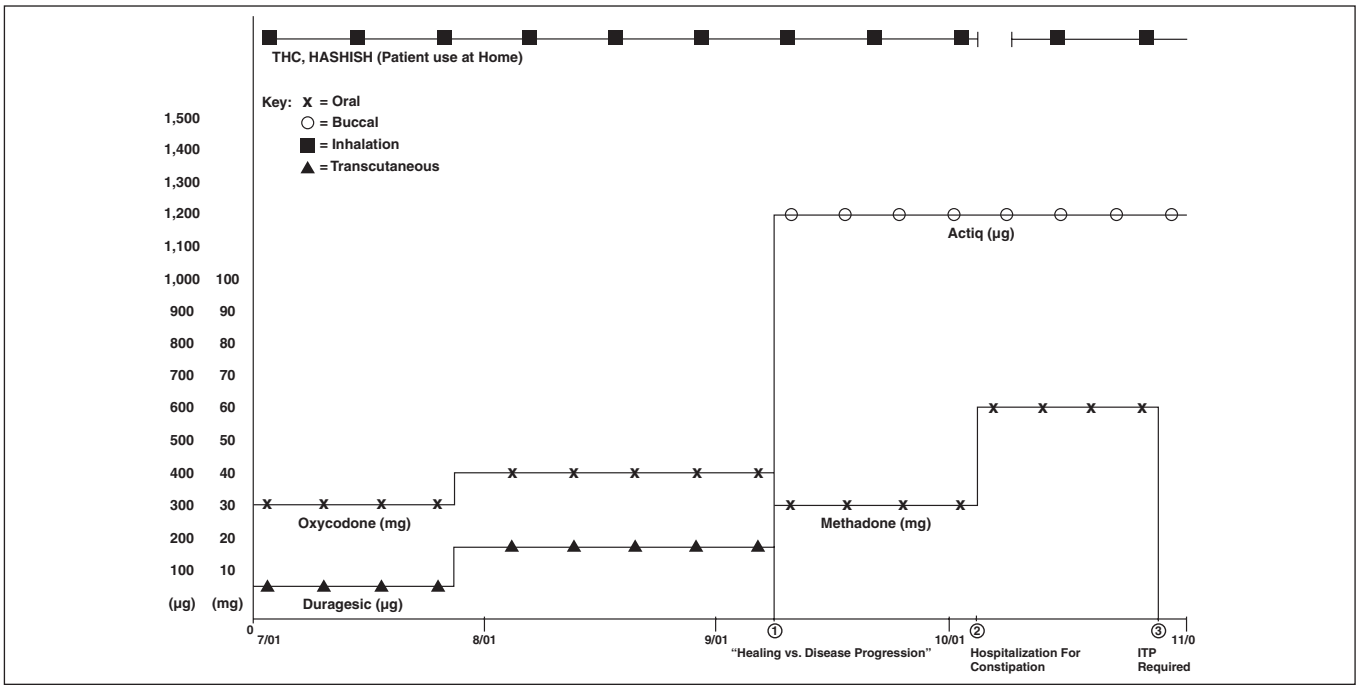
PAIN MEDICATION RECORD

Date	Mode	Medicine	Dosage/24 h	Response pain scale 0-10
7/30	TD	Durogesic	150 μg/72 h	5/10
	PO	Percocet (Oxycodone)	40 mg	
9/15	PO	Methadone	30 mg	7/10
	SL	Actiq	1,200 μg BID	Constipation
10/05	PO	Methadone	60 mg	2/10
	SL	Actiq	1,200 μg BID	
	PO	Methadone	60 mg	5/10
	SL	Actiq	1,200 μg BID	Constipation
	PO	Gabatril	4 mg	qhs
10/29	ITT	MS	3 mg	2/10
10/31	ITP	MS	3 mg	2/10
	PO	Oxycodone	20 mg	
11/4	ITP	MS	4 mg	4/10
11/19	ITP	MS	6 mg	6/10
11/24	ITP	MS	6 mg	8/10
	PO	Dilaudid	20 mg	
12/4	ITP	MS	11 mg	8/10
	PO	Dilaudid	40 mg	
12/16	ITP	MS	13 mg	5/10
	IV Bolus	Dilaudid	32 mg	
12/26	ITP	MS	15 mg	8/10
	IV PCA	Dilaudid	96 mg	
	SL	Actiq	2,400 μg	
12/27	ITP	MS	18 mg	8/10
	IV PCA	Dilaudid	86 mg	
	IV Bolus	Dilaudid	32 mg	
12/29	ITP	MS	25 mg	8/10
	IV PCA	Dilaudid	124 mg	
	IV Bolus	Dilaudid	24 mg	
12/31	ITP	Dilaudid	5 mg	5/10
	IV PCA	Dilaudid	154 mg	
1/3	ITP	Dilaudid	6 mg	10/10
	IV Bolus	Dilaudid	168 mg	
	IV PCA	Dilaudid	108 mg	

Date	Mode	Medicine	Dosage/24 h	Response pain scale 0-10
1/4	ITP	Dilaudid	12 mg	5/10
	IV Bolus	Dilaudid	224 mg	
1/5	IV PCA	Dilaudid	164 mg	
	ITP	Dilaudid	14 mg	5/10
1/6	IV Bolus	Dilaudid	100 mg	
	ITP	Dilaudid	16 mg	6/10
	IV PCA	Methadone	70 mg	
1/8	PO	Klonapin	1 mg	
	ITP	Dilaudid	18 mg	8/10
1/9	IV PCA	Methadone	124 mg	Sleepy/ arousable
	ITP	Dilaudid	20 mg	8/10
1/10	IV PCA	Methadone	150 mg	Stuporous/ arousable
	ITP	Dilaudid	25 mg	6/10 Sleepy
1/13	IV PCA	Methadone	62 mg	
	ITP	Dilaudid	25 mg	6/10 Sleepy
	IV PCA	Methadone	50 mg	
	IVSP	Propofol	100 mg	
1/15	ITP	Diaudid	25 mg	10/10
	IV PCA	Methadone	125 mg	Alert
1/16	ITP	Diaudid	25 mg	5/10
	IV PCA	Methadone	195 mg	Stuporous
1/17	ITP	Methadone	6 mg	5/10
	IV Bolus	Katamine	240 mg	Alert
	IV PCA	Methadone	300 mg	Stuporous
1/18	ITP	Methadone	12 mg	5/10
	IV PCA	Methadone	351 mg	Alert/ stuporus
1/20	ITP	Methadone	16 mg	5/10
	IV PCA	Methadone	688 mg	Sleepy/ arousable
1/21	ITP	Methadone	16 mg	Alert
	IV PCA	Methadone	670 mg	Sleepy

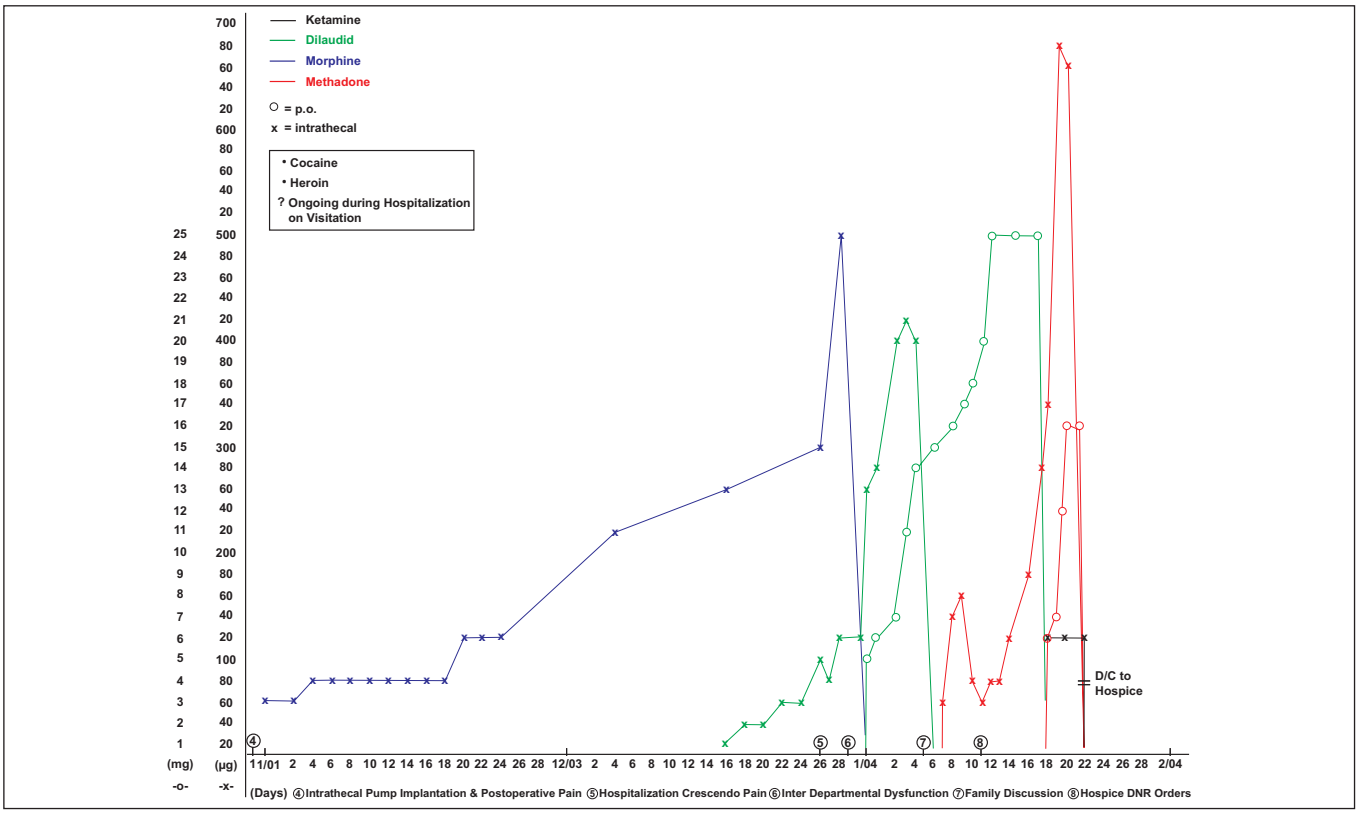
Appendix 3

JULY 1, 2004 TO NOVEMBER 1, 2004



Appendix 4

NOVEMBER 1, 2004 TO JANUARY 22, 2004



Appendix 5

ANESTHESIA–BASED PAIN MEDICINE, PALLIATIVE CARE, AND ONCOLOGY COMMONLY HEARD STEREOTYPES

Anesthesia-based pain medicine SVC	Palliative care SVC	Oncology SVC
1. Needle jockies	1. "Candy store" owners	1. Takeover mentatality
2. Cowboys	2. Knee jerk/dogmatic rejection of any interventional technology	2. Don't know when to stop
3. Lazy	3. Bureaucratic. Lacking creativity in problem solving	3. Unwilling to discuss or continually review the risk/benefit ratios of therapy
4. Not too bright	4. Arrogant—distrusts both interventionists and oncologists as being narrowminded	4. "Palliative" and "incurable disease" forbidden words
5. Economically motivated	5. Quick to blame	5. Unable to accept imperfection and own mortality. Death suggests personal defeat
6. "Hit and run" docs		
7. Disinterested or incapable of understanding "the big picture"		