ORIGINAL ARTICLE

Effectiveness and tolerability of tapentadol sustained release in the Australian setting

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ABSTRACT

Objective: *To assess the effectiveness and tolerability of tapentadol sustained release (SR) following its introduction to the Australian private market.*
Design: *A retrospective audit of routine clinical practice with data collection beginning 2 months after the first tapentadol SR prescription.*
Setting: *A multidisciplinary Australian pain clinic.*
Patients: *Fifty patients who were prescribed tapentadol SR as part of routine clinical management at the pain clinic.*
Interventions: *Trial of tapentadol SR with subsequent dose titration if the patient was satisfied with or tolerant of the medication.*
Main outcome measures: *Patient-reported pain outcome, side effects, medication adherence, and concomitant analgesic medications.*
Results: *Sixty-eight percent of patients reported major reductions in pain. Seventy-two percent of patients tolerated and adhered to treatment and 76 percent reported no side effects. Pain outcome was independent of pain type and prior opioid exposure; however, patients taking tapentadol in combination were more likely to report a positive outcome (Pearson $\chi^2 = 9.867$, $n = 46$, $p = 0.0072$).*
Conclusions: *Tapentadol was effective and generally well tolerated in the majority of patients for neuropathic, nociceptive and mixed pain types and this was regardless of prior opioid use.*

INTRODUCTION

The use of opioids for managing persistent pain has a history that goes back into antiquity, to the discovery and use of the opium poppy and its analgesic properties. Sumerian writings on the subject would indicate that the opium poppy has probably been used more than 5000 years[1] and it was around 200 years ago that morphine was first isolated from opium.[2] While morphine is the archetypal opioid, it rapidly became clear that in patients with persistent pain, an established palette of opioid choices allowed the selection of the optimal opioid for an individual considering that there are often idiosyncrasies in patients' responses to particular opioids.

Tramadol was the first of a new class of opioid analgesics to be released for some time and has been available in Australia since late 1998. Tramadol has a triple mode of action as a μ-opioid agonist, a noradrenaline inhibitor and a serotonin release enhancer, hence acting to modulate both ascending and descending nociceptive pain signaling pathways.[3] Numerous studies have demonstrated its efficacy, however, when combining tramadol with medications with a serotonergic effect, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), a serotonin syndrome may develop, albeit rarely.[4-7]

Tapentadol is a molecule with some structural similarity to tramadol but different pharmacological characteristics; tapentadol has only two synergistic mechanisms, with more potent μ-opioid agonist activity and noradrenaline reuptake inhibition activity, while lacking effects on serotonergic reuptake.[8]

This should enable safe combination with agents such as TCAs and SSRIs, which are widely used within the chronic pain population. There are a number of other features that make tapentadol more attractive as an analgesic, with a low likelihood for drug-drug interactions. Tapentadol is in itself the active drug with no active metabolites, unlike tramadol, which is a prodrug whose μ-opioid agonist effects are dependent on Cytochrome P450 2D6 phenotype and the risk of retention of the active metabolite M1 in renal failure.[8,9]

Tapentadol immediate release tablets were approved by the Food and Drug Administration for the treatment of chronic painful diabetic neuropathy in November 2008, and a sustained release (SR) form (called extended release in the United States) was approved in August 2011 for the treatment of mild to severe chronic pain.[10] Tapentadol SR was approved by the Therapeutic Goods Administration and released in Australia in February 2013. Recent studies have shed more light on its mechanism of action, such as a study in a mouse model of diabetic neuropathy, which showed that the antihyperalgesic efficacy of systemically administered tapentadol is based on the significant synergy of spinal and supraspinal effects of μ-opioid agonism and noradrenaline reuptake inhibition.[11] In a model of experimental neuropathic pain in Sprague-Dawley rats, tapentadol treatment induced elevated spinal noradrenaline.[12] An acute activation of alpha-2 adrenoreceptors was seen in single unit extracellular recordings of locus coeruleus neurons, in which the neural response to pain-like stimulation was inhibited by tapentadol.[13] Tapentadol has also been shown to be antihyperalgesic in animal models; in a chronic nerve constriction injury model in rats, the effect of repeated morphine doses to relieve allodynia vanished over a 4-day treatment period, while this effect was maintained with tapentadol.[14]

Clinically, primary efficacy of tapentadol SR in chronic pain has been documented in several randomized double blind placebo controlled studies; a pooled analysis of these studies has documented statistically and clinically significant improvement over placebo.[15] Numerous clinical studies have also reported comparable analgesia, but improved tolerability for tapentadol in comparison to oxycodone, particularly in relation to gastrointestinal side effects including nausea, vomiting, and constipation.[10,16] A recent randomized, controlled, open-label study compared tapentadol SR to oxycodone/naloxone SR, an opioid agonist/antagonist combination aimed to address gastrointestinal side effects, and found tapentadol SR to have superior efficacy and tolerability.[17] Furthermore, data relating to the significantly reduced affinity to the μ-opioid receptor of tapentadol in comparison to morphine and other opioids[18] show a reduced risk of opioid tolerance development, opioid induced hyperalgesia and lower abuse potential seems possible. This assumption is supported by data on tapentadol use in the United States; a meta-analysis of two databases estimated the risk of opioid abuse to be 65 percent lower with tapentadol than with oxycodone.[19] Data from a survey program of college students found that nonmedical use of tapentadol immediate release was low and decreased over time after a short-lived experimental phase following the release of tapentadol.[20]

Very limited data have been published on the clinical use of tapentadol in the Australian setting, although they have been well documented in Europe.[21-23] Here, we provide a prospective "real world" postmarket study that follows patients treated in an Australian clinical setting for chronic pain with tapentadol SR, subsequent to its release on the private market, to assess its efficacy and tolerability.

METHODS

Subsequent to the clinical introduction of tapentadol SR to the Australian market in February 2013, and with approval from the Bellberry Human Research Ethics Committee, an audit was conducted on the first 52 patients treated at a large, private multidisciplinary pain clinic in New South Wales, Australia. Tapentadol SR is available in Australia as Palexia® SR; a registered trademark of Grünenthal Pty Ltd. Palexia® SR is distributed by bioCSL (Australia) Pty Ltd under license from Grünenthal Pty Ltd.

Subjects

Fifty patients were prescribed tapentadol as part of routine clinical management. Patients were selected for tapentadol therapy for either of the following reasons: 1) having failed to respond to other opioids, 2) having experienced intolerable side effects on prescribed opioids, or 3) because the mixed nociceptive + neuropathic pain profile of the patient potentially made tapentadol the opioid of

choice for them in de novo prescription. Informed consent for use of information for research and quality assurance programs was obtained from all patients.

Data collection

Patients were followed up per standard practice and patient health status. Patients were asked, either in person during consultation at the clinic or via telephone, whether they had experienced a "major or significant" improvement to their pain. Data collection was commenced 2 months after the first tapentadol prescriptions were administered and continued for a further 2 months, after which patients continued with routine therapy. A detailed report was made for each patient comprised of demographical information, cause and type of pain (including clinical diagnosis of nociceptive, neuropathic, or mixed pain), history of opioid medications, the last medication taken prior to tapentadol commencement, indication for tapentadol administration, tapentadol adherence, patient-reported pain outcomes, combined medications, and tapentadol-related adverse effects.

Data analysis and statistics

Data for 50 patients were analyzed. Basic analysis, such as means and percentages, was performed within Microsoft Excel. Statistical tests were performed using the JMP Statistical Discovery software (version 10.0.0; SAS Institute, Cary, NC). Observational reporting and descriptive analysis was performed otherwise.

RESULTS

Patient demographics

The results presented here are for a cohort of 50 patients. A summary of the demographical information is presented in Table 1. The cohort consisted of 56 percent males, with a mean age of 43.40 (±11.39), and 44 percent females, with a mean age of 48.41 (±12.18), and an overall mean age of 45.55 (±11.68). Patients were classed according to the type of pain from which they are suffering, whether neuropathic (46 percent), nociceptive (14 percent), or mixed pain (40 percent) (Figure 1A). For a detailed list of diagnoses/causes of pain, please refer to Appendix 1. The number of opioids taken prior to tapentadol was none (10 percent), 1 (30 percent), 2 (22 percent), and ≥3 (38 percent) (mean = 2.26 ± 1.14). Common prior opioids included oxycodone slow release (n = 21), codeine/paracetamol or codeine/ibuprofen combinations (n = 17), tramadol (n = 16), and buprenorphine (n = 16).

Table 1. Summary of tapentadol cohort demographical information (n = 50)

Demographics	N	Percent
Gender		
Male	28	56
Female	22	44
Age (mean)	45.55 ± 11.68	
Male	43.40 ± 11.39	
Female	48.41 ± 48.41	
Pain type		
Neuropathic	23	46
Nociceptive	7	14
Mixed pain	20	40
Prior opioids		
None	5	10
1	15	30
2	11	22
≥3	19	38
Indication for tapentadol		
Alternative analgesic required	20	40
Adverse drug effects	16	32
Additional analgesic required	7	14
Other	7	14

Data are presented as number of patients and percentage, except for age, which is presented as mean ± standard deviation.

Commencement of tapentadol

The most common indication for administration of tapentadol was the requirement for an alternative

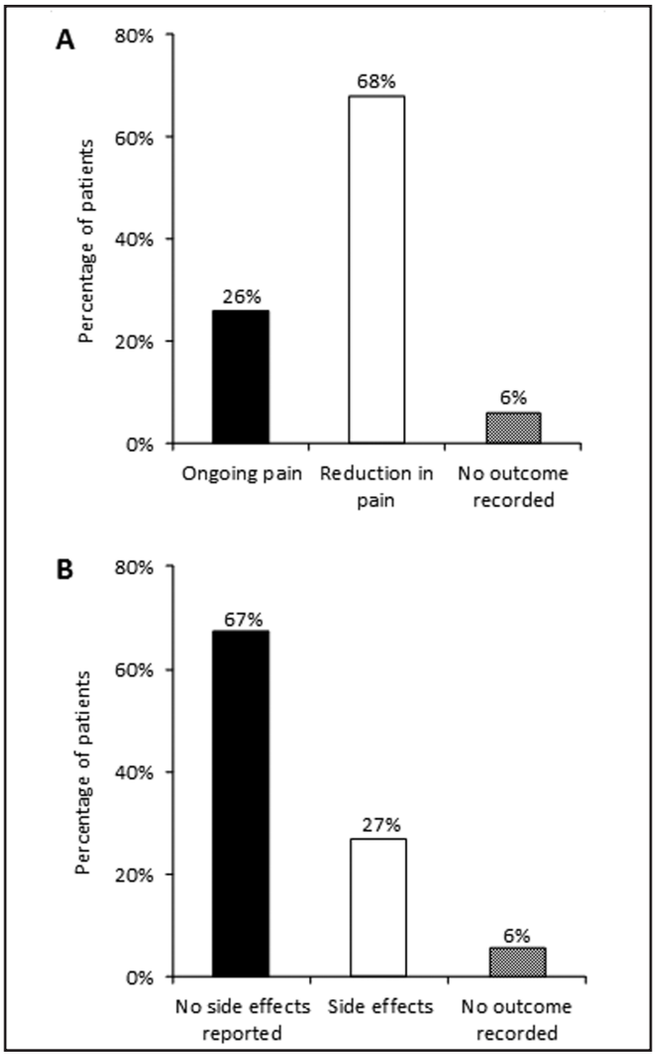

Figure 1. Summary of tapentadol treatment outcomes (n = 50). (A) Effect on pain intensity and (B) reported side effects.

analgesic due to poor responsiveness to the current analgesic (40 percent). This included cases where there was no response or minimal response to a trialed opioid, cases where the patient was currently using an opioid and experiencing a loss of efficacy or developing signs of opioid tolerance (in which case opioid rotation may have been directed), and in cases where the patient was not responding to prior nonopioids, yet was a poor candidate for pure opioids. Other reasons included adverse drug effects from other opioids (32 percent) and the requirement for an additional analgesic as part of combination therapy to maximize pain relief (14 percent), with the remainder having other reported reasons (such as opioid detoxification) or no recorded reason (Table 1). The mean initial dose of tapentadol was 98.00 mg (±54.36) and the mean final dose was 221.25 mg (±51.75). The minimum dose was 50 mg (mane) and the maximum dose was 250 mg (bid).

Combined medications

A total of 35 patients (70 percent) were taking tapentadol in combination with other analgesic medications, including opioids (30 percent, n = 15/50—particularly transdermal buprenorphine low dose or immediate release oxycodone for breakthrough analgesia), pregabalin (24 percent, n = 12/50), and serotonergic-noradrenaline reuptake inhibitors (6 percent, n = 3/50). Tapentadol was added to prior medications in cases where partial analgesia was obtained without side effects, to achieve greater pain relief. The mean number of medications combined with tapentadol was 1.08 ± 0.96.

Efficacy and tolerability

Overall, it appears in this population that tapentadol had a high efficacy, with 68 percent of patients reporting a major reduction in pain (Figure 1A). Tapentadol appears to be well tolerated, with 72 percent (n = 36/50) of patients adhering to tapentadol and 76 percent (n = 38/50) of patients not experiencing any adverse drug effects (Figure 1B). Of the 15 patients with adverse effects to previous opioids, 12 patients (80 percent) reported no side effects associated with tapentadol. The average duration of usage was 84.42 (±44.06) days, with 14 patients (28 percent) having ceased tapentadol due to lack of pain relief or side effects. A minority of patients (28 percent, n = 14/50) experienced side effects on tapentadol, including nausea, vomiting and/or drowsiness (12 percent), and leg cramping or pain and weakness (4 percent). Five patients (10 percent) experienced central nervous system (CNS) effects, including cognitive effects, behavioral changes, and one with hallucination. Of the 35 patients taking combined medications, six patients suffered side effects. There were a total of four patients for which pain efficacy outcomes were not reported; two of these were lost to follow-up and two ceased tapentadol early due to side effects.

Potential factors affecting outcomes

Tapentadol demonstrated efficacy for all types of pain. A major reduction in pain was recorded for 65 percent of patients diagnosed with neuropathic pain

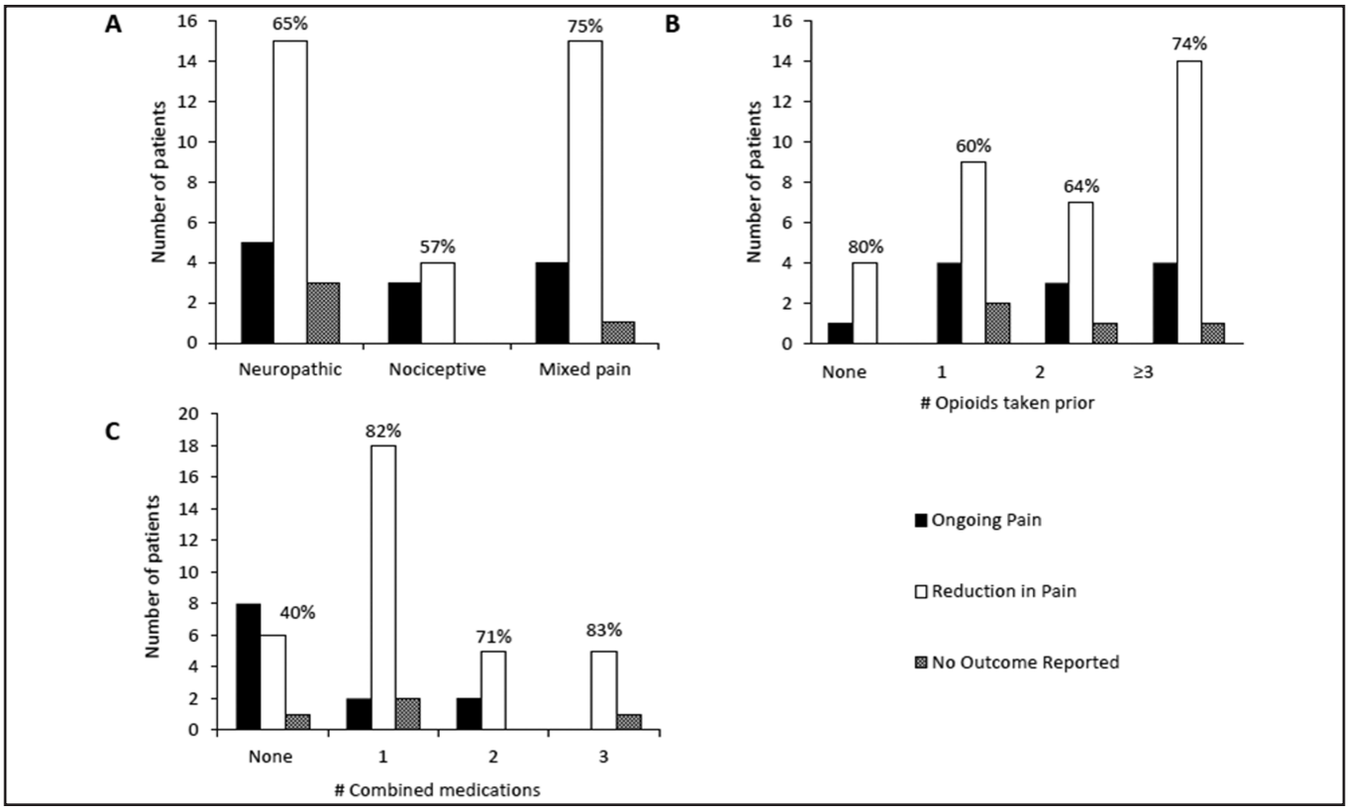

Figure 2. Tapentadol treatment pain outcomes for patients grouped by (A) type of pain; (B) number of opioids taken prior to tapentadol; and (C) number of combined medications. Data presented as number of patients. Labels represent the percentage of patients with major reductions in pain per category (n = 50).

(n = 15/23), 57 percent of patients diagnosed with nociceptive pain (n = 4/7), and 75 percent of patients with mixed pain (n = 15/20) (Figure 2A). Major reductions in pain were reported for patients regardless of the degree of prior opioid exposure (Figure 2B). Pain outcome was not statistically dependent on the type of pain, nor the number of prior opioids. However, there was a significant relationship (dependence) between pain outcome and the number of combined medications (Pearson $\chi^2 = 9.867$, n = 46, p = 0.0072; please refer to the Appendix for the contingency analysis results: Appendix 2A–2C). Most patients on combination therapy (>70 percent in each group) reported a major reduction in pain compared to patients taking tapentadol alone (>50 percent) (Figure 2C).

DISCUSSION

This study assesses the clinical use of tapentadol in a "real world" setting following the introduction of tapentadol to the Australian private market. The results of this study provide support for the efficacy and tolerability of tapentadol treatment in patients of various pain types and with varying degrees of previous opioid exposure and combination medications. In this study, tapentadol had a relatively high success rate that was independent of pain type and previous opioid treatment. Tapentadol has been shown to be efficacious for neuropathic tumor-related pain,[24] osteoarthritis pain,[15,23] low back pain, including low back pain with a neuropathic component,[17,21,25] and chronic pain in general.[22] Each of these studies reported high levels of tolerability and adherence to tapentadol treatment.

Similar to previous studies, tapentadol was well tolerated in the current investigation. The majority (72 percent) of patients adhered to treatment, continuing to take tapentadol after the data collection period. More than 75 percent of patients did not experience any side effects, including those taking additional medications. The majority of patients (80 percent) who reported side effects on prior opioids did not report any side effects while taking tapentadol. None of the patients who were concomitantly taking serotonin-noradrenaline reuptake inhibitors

(SNRIs) experienced additional side effects with the addition of tapentadol. Four patients experienced CNS side effects, though none of these patients was taking serotonergic medications. Previous studies that have allowed concomitant use of serotonergic antidepressants have reported a safety profile similar to patients that were not taking such medications.[22,23,26] This is in line with the presumption that serotonergic side effects should be less likely with tapentadol than with tramadol due to it having reduced effect on serotonin reuptake.[26]

In this study, many patients reported significant improvement in pain with tapentadol when switching medications. There was no statistical relationship between tapentadol efficacy and the number of prior opioids. Statistical analysis did, however, indicate a significant relationship between tapentadol efficacy and the number of combined medications. Patients combining tapentadol with other analgesic medications were more likely to report a major reduction in pain, which suggests that, in a population such as patients attending a pain clinic, tapentadol is most effective in combination therapy. Most patients taking tapentadol in combination did not report side effects and this provides support for the safety and tolerability of tapentadol in combination therapy.

This study has obvious limitations pertaining to the fact that it was conducted in the "real world" setting. The moderate size of the cohort is a consequence of the short study period (5 months) and that it was conducted at a single clinic. Further limitations pertaining to the real world setting were the lack of a control and the absence of inclusion and exclusion criteria; that is, the pain physician prescribed tapentadol only if it was deemed the most appropriate medication, and did not prescribe tapentadol over treatments that were thought to be more appropriate; patients were also allowed to continue additional medications if it was felt that this would produce optimal pain relief, all of which reflect routine clinical practice. Current guidelines also recommend combination therapy for patients with neuropathic pain.[27] It is uncommon that patients present to a clinic without having already tried opioids or other analgesic medications, and many patients present to a clinic while already on medications in search of additional treatment. The advantages of studying a "real world" patient population include avoiding issues of selectivity and population bias. Studies such as this complement controlled clinical studies and are valuable in the context of pharmacovigilance.

CONCLUSION

The results of this "real world" investigation confirm the current literature supporting the efficacy and tolerability of tapentadol SR for numerous pain classifications, particularly neuropathic and mixed pain, and in various medication combinations, in an Australian standard care setting.[15,17,21-25,28] The results presented here also suggest that the efficacy of tapentadol SR is not associated with prior opioid exposure. Taken together with the demonstrated noninferior efficacy and improved tolerability over previous generation opioids, it is plausible to conclude that tapentadol may be considered a valid alternative to previous generation opioids in the treatment of chronic pain.

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Conflict of interest/financial disclosure statement: Dr. Marc Russo was previously a member of the Scientific Advisory Board (SAB) of Grünenthal and has received SAB honoraria. Tapentadol SR is available in Australia as Palexia® SR; a registered trademark of Grünenthal Pty Ltd. Palexia® SR is distributed by bioCSL (Australia) Pty Ltd under license from Grünenthal Pty Ltd. No payments were received for any aspect of the work presented in this manuscript. The raw data formed part of a previous PBS listing submission.

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Appendix 1

DETAILED PATIENT DEMOGRAPHICS

M/F	Age	Cause of pain	Type of pain
M	42	Headaches relating to myofascial pain with cervical nerve root irritation	Mixed type
M	40	Right upper limb pain due to central nerve root or spinal cord stretch	Mixed type
M	28	Failed back surgery syndrome, with neuropathic leg pain and nociceptive low back pain	Neuropathic
F	23	Right sided cervicobrachialgia with prominent neuropathic features	Neuropathic
M	23	Radiating pain into left arm due to symptomatic internal disc disruption	Neuropathic
F	49	Visceral hyperalgesia due to central sensitization of spinal cord	Neuropathic
M	62	Refractory pain: active zygapophyseal joint arthralgia	Mixed type
M	47	Neuropathic and nociceptive pain due to spinal osteomyelitis	Mixed type
F	47	Neuropathic low back pain and leg pain secondary to epidural fibrosis	Neuropathic
F	48	Sacral pain arising from superior aspect of the sacroiliac joint with referred pain to lumbar spine at L5/S1 disc	Neuropathic
F	67	Pain post total knee replacement	Nociceptive
F	38	Bilateral shoulder pain	Mixed type
M	49	Complex Regional Pain Syndrome type I of the lower left limb	Mixed type
F	49	Persistent pain evident to myofascial pain	Neuropathic
M	40	Low back pain related to discogenic pain and right shoulder pain	Mixed type
M	58	Neuropathic pain in the left knee. Likely to have Complex Regional Pain Syndrome type 1	Neuropathic
M	34	Persistent knee pain that is neuropathic in nature	Neuropathic
M	51	Symptomatic thoracolumbar spondylosis with scoliosis. Anterior thigh pain is neuropathic	Neuropathic
M	62	Both nociceptive pain from cervical spondylosis and neuropathic pain from his cord gliosis	Mixed type
F	54	L5 radicular pain with radiating pain down the left leg. Ongoing sciatica	Neuropathic
M	37	Chronic daily headaches secondary to opioid intake. Persistent neck pain due to nociceptive and myofascial pain	Nociceptive
F	51	Bilateral neuropathic low back pain and bilateral neuropathic leg pain	Neuropathic
M	42	Neuropathic pain as well as combination	Mixed type
F	50	Neuropathic pain: failed back surgery syndrome	Neuropathic
F	42	Mixed nociceptive/neuropathic ankle and foot pain	Mixed type
F	52	Myofascial pain, with probable symptomatic thoracic spondylosis	Mixed type
F	60	Complex Regional Pain Syndrome type I of the right limb	Mixed type
M	37	Neuropathic pain with persistent right leg pain. Nociceptive pain with persistent low back pain	Mixed type
M	36	Left sided sciatica related to L5 nerve root compression	Neuropathic

DETAILED PATIENT DEMOGRAPHICS (continued)

M/F	Age	Cause of pain	Type of pain
F	33	Neuropathic pain of the left ankle	Neuropathic
F	40	Symptomatic lumbar spondylosis involving facet joints	Nociceptive
M	38	Thoracic paravertebral muscle spasm	Mixed type
F	63	Multisite pain in both shoulders	Mixed type
F	41	Neuropathic pain with features of Complex Regional Pain Syndrome	Neuropathic
F	64	Severe back pain consistent with myofascial and nociceptive features	Nociceptive
M	32	Symptomatic internal disc disruption at L5/S1 disc causing low back pain	Neuropathic
F	63	Neuropathic anterior knee pain	Neuropathic
M	63	Symptomatic lumbar spondylosis arising from disc disruption	Mixed type
M	51	Discogenic pain of the lower back	Nociceptive
M	55	Mixed nociceptive/neuropathic pain	Mixed type
M	47	Mid facial pain that is neuropathic in nature	Neuropathic
F	25	Traumatic L5/S1 disc disruption leading to low back pain	Nociceptive
M	38	Refractory neuropathic pain in the arm	Neuropathic
M	28	Labral tear presenting with post-traumatic hip pain	Nociceptive
F	44	Ongoing abdominal pain	Neuropathic
M	29	Nociceptive and neuropathic pain of the lower back and bilateral legs	Mixed type
M	35	Bilateral cervicobrachialgia	Mixewd type
M	54	Radicular pain causing low back pain, neck pain, and headaches	Mixed type
M	57	Neuropathic pain due to symptomatic lumbar spondylosis as well as bilateral inguinodynia	Neuropathic
F	62	Radicular pain due to large compressive L4/5 disc	Neuropathic

Appendix 2

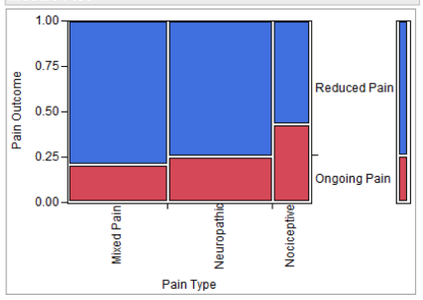
CONTINGENCY ANALYSIS RESULTS (MOSAIC PLOTS, CONTINGENCY TABLES, AND INDEPENDENCE TESTS) GENERATED/PERFORMED BY THE JMP STATISTICAL DISCOVERY SOFTWARE (VERSION 10.0.0; SAS INSTITUTE, CARY, NC): (A) PAIN OUTCOME VS PAIN TYPE; (B) PAIN OUTCOME VS NUMBER OF PRIOR OPIOIDS; AND (C) PAIN OUTCOME VS NUMBER OF COMBINED MEDICATIONS (RED BOX HIGHLIGHTS SIGNIFICANT TEST RESULT AT THE LEVEL OF P < 0.01).

A

Contingency Analysis of Pain Outcome By Pain Type

Freq: Count

Mosaic Plot



Contingency Table

Pain Outcome

Pain Type	Count / Total % / Expected	Ongoing Pain	Reduced Pain	
Mixed Pain		4	15	19
		8.70	32.61	41.30
		4.95652	14.0435	
Neuropathic		5	15	20
		10.87	32.61	43.48
		5.21739	14.7826	
Nociceptive		3	4	7
		6.52	8.70	15.22
		1.82609	5.17391	
		12	34	46
		26.09	73.91	

Tests

N	DF	-LogLike	RSquare (U
46	2	0.59689684	0.022

Test	chi-square	Prob>ChiSq
Likelihood Ratio	1.194	0.5505
Pearson	1.283	0.5265

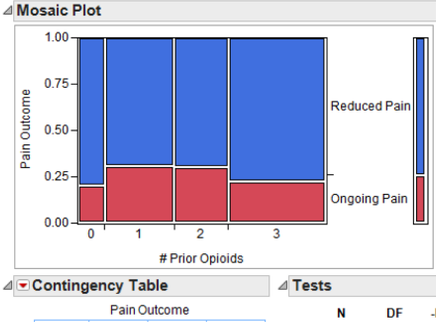
Warning: 20% of cells have expected count less
chi-square suspect.

B

Contingency Analysis of Pain Outcome By # Prior Opioids

Freq: Count

Mosaic Plot



Contingency Table

Pain Outcome

#Prior Opioids	Count / Total % / Expected	Ongoing Pain	Reduced Pain	
0		1	4	5
		2.17	8.70	10.87
		1.30435	3.69565	
1		4	9	13
		8.70	19.57	28.26
		3.3913	9.6087	
2		3	7	10
		6.52	15.22	21.74
		2.6087	7.3913	
3		4	14	18
		8.70	30.43	39.13
		4.69565	13.3043	
		12	34	46
		26.09	73.91	

Tests

N	DF	-LogLike	RSquare (U)
46	3	0.23285688	0.0088

Test	chi-square	Prob>ChiSq
Likelihood Ratio	0.466	0.9264
Pearson	0.463	0.9270

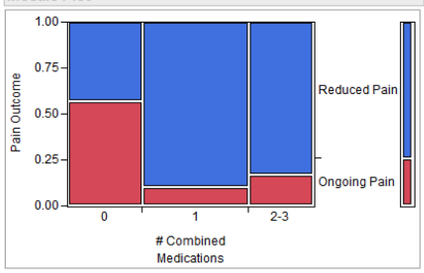
Warning: 20% of cells have expected count less than 5,
chi-square suspect.

C

Contingency Analysis of Pain Outcome By # Combined Medications

Freq: Count

Mosaic Plot



Contingency Table

Pain Outcome

# Combined Medications	Count / Total % / Expected	Ongoing Pain	Reduced Pain	
0		8	6	14
		17.39	13.04	30.43
		3.65217	10.3478	
1		2	18	20
		4.35	39.13	43.48
		5.21739	14.7826	
2-3		2	10	12
		4.35	21.74	26.09
		3.13043	8.86957	
		12	34	46
		26.09	73.91	

Tests

N	DF	-LogLike	RSquare (U)
46	2	4.9332592	0.1868

Test	chi-square	Prob>ChiSq
Likelihood Ratio	9.867	0.0072*
Pearson	10.239	0.0060*

Warning: 20% of cells have expected count less than 5,
chi-square suspect.