Benzodiazepines may be worse than opioids: negative medication effects in severe chronic pain.

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Abstract

Objectives

Opioid prescription for non-malignant pain is increasing in Europe and the US. Research and guidance have focused on the potential for dependency and medical side effects with high doses. In contrast, benzodiazepines have received little attention in the chronic pain literature, despite evidence for dependency and cognitive impairment in long term use. We aimed to examine the relationship between these classes of medication use, mood and functioning.

Methods

This cross sectional study included patients (N = 229) with disabling chronic pain who were about to start intensive pain rehabilitation. They completed self-report measures of mood, functioning and responses to pain. We examined each patient's medication use and calculated a single Morphine Equivalent (ME) dose per person, and a similar Diazepam Equivalent (DE) dose. We examined the relationship between drug dose, mood and functioning.

Results

Higher DE doses were associated with worse outcomes in most domains. Higher ME doses were more narrowly associated with worse functioning. There was no evidence for any benefit of these drugs; higher doses were not associated with less pain, fear or disability. Higher ME doses were not more problematic, contrary to our predictions. The combination of opioids and benzodiazepines was associated with particularly poor outcomes for mood.

Discussion

This study is the first to examine both opioid and benzodiazepine use together in chronic pain. We found the anticipated negative effects of opioid medication, and particularly consistent associations between benzodiazepine use and poor wellbeing. Future guidance on chronic pain prescription should focus on restricting benzodiazepine use.

Key Words: Chronic pain, Opioids, Benzodiazepines, Mood, Disability

Introduction

Opioid analgesics are recognised as a potentially useful treatment for non-malignant chronic pain. However, there is also much concern about the consequences of long term, or high dose, prescription of opioids in chronic pain[1]. Although opioids may in some cases be under-prescribed, for example, in palliative care settings and in developing world contexts, Zin et al. (2014) have described a "huge" (p. 1343) increase in strong opioid prescription for non-malignant pain in the UK between 2000 and 2010[2].

It is widely agreed that opioid doses of greater than 120mg per day are hard to justify in non-malignant pain and greatly increase risk of overdose[1,3]. Long term opioid use may cause immune deficiency, endocrine dysfunction and hyperalgesia[4]. Despite guidance indicating that strong opioids should be used with care with patients who are vulnerable to addiction, a process of 'adverse selection' seems to result in high doses of opioids being prescribed to those with psychopathology and proneness to substance misuse[4,5]. Higher opioid doses have been found to be associated with greater pain, depression and health service use[6,7].

Opioid prescription has become a focus of scrutiny in the chronic pain literature, and comprehensive prescribing guidelines are available. In contrast, the pain literature only infrequently engages with issues of benzodiazepine prescription. Benzodiazepines are often prescribed to patients with pain as muscle relaxants, and they may have a role in acute back pain[8]. However, in the broader medical and psychiatric literature there is concern about the use of benzodiazepines and the pharmacologically similar 'Z-drugs' (i.e. Zopiclone, Zolpidem; we will include these under the broader heading of 'benzodiazepines'). Guidance restricts their use for anxiety and insomnia to strict, brief periods of 2-4 weeks[9]. It is widely accepted that benzodiazepines can be associated with dependency and that they can be hard to

discontinue. Long-term users of benzodiazepines have clear cognitive deficits[10], and the acute effects of benzodiazepines can include sedation, dysphoria and cognitive impairment such as memory problems[11].

Although clinicians may prescribe benzodiazepines as 'muscle relaxants' for back pain [12], patients with chronic pain may instead use them as anxiolytics and hypnotics. In chronic pain, it is unclear whether prescribers regard themselves as bound by the 2-4 week prescription limits that are recommended in other fields of medicine. Benzodiazepines are sometimes prescribed alongside opioids, despite evidence that they antagonise opioid analgesia[13]. Thus, there is no evidence that benzodiazepines help with the core symptoms of chronic pain, and substantial evidence for harm in long term use; ostensibly short term prescriptions regularly convert into persistent use[12].

Previous research has focused on how patients become dependent on opioids and other compounds (e.g. Elander et al., 2014[14]). However, in this study, we examined the impact of these opioids and benzodiazepines on functioning and mood. We created standardised 'morphine equivalent' and 'diazepam equivalent' doses for each individual patient and examined their cross-sectional associations with validated measures of mood and functioning.

Materials and Methods

Participants

Participants in this cross-sectional study were 229 working-age adults who were consecutively starting treatment, which was intensive chronic pain rehabilitation. They were seen at a national specialist service that is dedicated to treating individuals with relatively long-standing and disabling pain. All patients being treated in the service were eligible for inclusion in the study; they had all been selected clinically as suitable for inclusion in group treatment.

Participants were 67% female and on average 46.7 years old (SD 10.2), with an average pain duration of 11.8 years. Most were not working due to pain (72%), and had not worked for an average of 5.6 years (SD 5.8 yrs, median 3.8 yrs). Participants had a substantial treatment history, seeing doctors around once per month for their difficulties (mean 5.5 visits in six months, median 4) and having seen on average 6.5 doctors for their pain (median 6). Participants recorded a mean of 1.85 surgeries for pain per person (36% ≥ 1 surgery; 24% ≥2 surgeries; 15% ≥ 3 surgeries). Despite the history of intervention, they rated their usual pain as 7.3 / 10 (SD 1.5, median 8.0; a one-off numerical rating scale of 'usual' pain). Participants were a diagnostically mixed group, selected by functional disability rather than through symptoms or source of pain; all had non-malignant musculoskeletal pain, with a range of different patterns and aetiologies. They were recruited consecutively, subject to consent, over a 2.3 year period (January 2009 – May 2011).

Assessment

On the first day of their treatment course, participants received a pack of questionnaires (described below). They gave informed, written consent to the use of these for research

purposes; use of these data for research purposes was approved by the relevant Research Ethics Committee and Hospital Research and Development Committee. They were given dedicated time to complete the questionnaires and the assistance of an assistant psychologist, if needed. These questionnaires were also administered at the end of treatment and to those patients who attended a follow up visit; these time points are not included in the current analysis. The questionnaire pack contained measures of clinically important variables such as depression, disability and pain-related fear, as well as instruments indexing psychological styles in the face of pain, such as pain acceptance. These are described below.

Measures of functioning and distress

Sickness Impact Profile (SIP[15])

The SIP is a behaviourally based measure of health status and daily functioning consisting of 136-items across 12 subscales. Respondents are asked to tick statements that describe them at the time of answering and are related to their state of health (e.g. "I am not doing heavy work around the house"). A weighted sum reflecting levels of disability is calculated for each subscale. Subscales can then be combined to calculate a (1) Total disability score, (2) a Physical disability score (from 'Ambulation', 'Mobility' and 'Body Care and Movement' subscales), and (3) a Psychosocial disability score (from 'Social', 'Alertness', 'Emotional' and 'Communication' subscales). It has excellent internal consistency ($\alpha = 0.92$) and good construct validity.

British Columbia Major Depression Inventory (BC-MDI[16])

The BCMDI is a 20-item self-report measure of depression modelled after the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (4th ed.: DSM-IV,

American Psychiatric Association, 1994). The first 16 of the items assess the presence of depressive symptoms over the past two weeks; they then assess their severity, which is rated on a 5 point scale ranging from 1 (*"very mild problem"*) to 5 (*"very severe problem"*). The final three items measure the impact of these symptoms on work/school, family and social activity on a scale of 0 (*"No impact on my day-to-day life") to 4 ("Very severe impact on my day-to-day life").* Thus the BCMDI generates scores for both symptom severity and symptom-related impairment of function. It has been shown to have a good sensitivity (*.92)* and specificity (*.99)* for detecting cases of Major Depressive Disorder.

Pain Anxiety Symptoms Scale (PASS[17])

The Pain Anxiety Symptoms Scale measures anxiety and fear responses that are specific to pain, for example, "pain sensations are terrifying". The version used here was the 20-item short form. Items are scored on a 6 point Likert scale ranging from 0 ("never") to 5 ("always").The PASS-20 has been shown to have good construct validity and strong internal consistency and reliability.

Chronic Pain Acceptance Questionnaire (CPAQ[18])

The CPAQ is a 20-item measure of acceptance of pain subdivided into the two components of activity engagement and pain willingness. These two components (1) indicate the extent to which activities are being performed in the presence of pain (e.g. "I lead a full life even though I have chronic pain") and (2) the respondent's willingness to relinquish any attempts to control or avoid pain (e.g. "I need to concentrate on getting rid of my pain" – reverse scored). Items are rated on a 6 point scale ranging from 0 (*"never true"*) to 6 (*"always true"*). The CPAQ has a satisfactory reliability of $\alpha = 0.78 - 0.82$

Acceptance and Action Questionnaire (AAQ-II[19])

The AAQ-II is a measure of general psychological acceptance; the version used in this study was the 10-item version of the AAQ-II, which has better psychometric properties than the AAQ-I. Items reflect the willingness of the individual to accept experiences of potentially unpleasant emotions, physical sensations or cognitions without attempting to change or avoid them or needlessly allow them to govern action (e.g. "It's OK if I remember something unpleasant"). Items are scored on a 7 point scale ranging from 1 ("never true") to 7 ("always true"). The measure has achieved good structure and construct validity ($\alpha = 0.84$) and good 3 and 12 month test-retest reliability ($\alpha = 0.81$ and $\alpha = 0.79$ respectively).

Chronic Pain Values Inventory (CPVI[20])

The CPVI is a 12-item measure of values based action for use with chronic pain populations. Items are distributed into the 6 domains of family, intimate relations, friends, work, health and growth and learning. Six items assess how much respondents value each domain and a further six assess their perceived success at living according to their values. Items are measured on a 6 point scale ranging from 0 ("not at all successful") to 5 ("extremely successful"). It has good internal consistency ($\alpha = 0.80$) and support for validity as a representation of values-based action from previous studies.

Calculation of morphine and diazepam-equivalent doses

Two sources of data around medication use were used; patients reported their medication regime in their questionnaire pack, and it was also recorded in clinical correspondence as part of their medical assessment. A research assistant undertook a notes review, recording all total daily opioid and benzodiazepine doses. Where there was a discrepancy between self-reported medication use and that recorded at medical assessment, the research assistant made a judgement about which seemed more reliable, supported by more experienced members of the research team (e.g. JGG). For example, if a patient wrote that

they used Diazepam 'only when I need it' on written questionnaires, but on close medical questioning they admitted using it three times per day on average, we would use the latter estimate. We made a distinction between how the drugs were prescribed, and how they were used; we focused on the latter.

We developed a table of morphine-equivalent (ME) doses – see Table 1 – from a range of different UK-based sources. There is dispute about morphine equianalgesic values[21], so these values were taken from relatively authoritative national guidance, but the precise values remain open to challenge. We used values from the British National Formulary[22], UK Medicines Information Service (NHS)[23], and British Pain Society Guidance[1]. For Diazepam-equivalent (DE) doses, we recorded equivalent doses for both benzodiazepines and Z-drugs. These values were taken from the UK Medicines Information Service[24], and the Oxford Specialist Handbook in Addiction Medicine[25] (see Table 2).

********** TABLES 1 and 2 ABOUT HERE, PLEASE **********

Statistical methods

We initially examined associations in between medication dose and mood / function using correlation coefficients (nonparametric where appropriate). We then addressed the issue of potential confounding variables using hierarchical multiple regression. We also used lumped patients into (1) those taking a class of drug versus (2) those not taking it, and used ANOVA to examine the impact of different combinations of drugs. Where we used ANOVA to explore between-group differences, post-hoc testing was needed to clarify exactly which groups differed from each other. There are a range of choices for post-hoc tests; we chose Tukey's HSD as it is widely used and we aimed to minimise the risk of a Type 1 error.

Results

Medication frequencies and doses

Eighty one percent of participants were on some form of opioid medication (81.2%), and 30.3% were on a benzodiazepine or Z-drug (we will use the term 'benzodiazepine' to refer to both). Over a quarter were taking both types of drug (28.1%). Dosages of each drug type can be seen in Figures 1 and 2; in both cases, distributions are positively skewed, with a minority taking high doses. Mean daily morphine equivalent (ME) doses were 109.6mg (SD 147.6); the range was 0mg to 749mg, and with the median dose of 48mg. Types of opioid preparation were as follows: 46.3% weak opioid[1] (e.g. Codeine, Dihydrocodeine), strong opioid[1] 28.4% (e.g. Morphine, Oxycodone, Fentanyl), sustained release 27.9% (patients were often on more than one opioid type). Diazepam-equivalent (DE) doses ranged between 0 and 40mg per day, with a mean of 3.2mg and a median of 0mg. High opioid doses were not uncommon; 27% of participants were on a ME dose of > 120mg per day. Of those on >120mg ME per day, 37% were also taking a benzodiazepine.

********** FIGURES 1 and 2 ABOUT HERE, PLEASE **********

Associations between dose and functioning

We examined associations between DE, ME and standardised measures of mood, functioning and psychological approach. Due to the non-normal distributions of DE and ME, non-parametric correlations were used throughout. Table 3 shows the correlations. Neither ME nor DE were associated with pain intensity; that is, on average, no increases in the quantities of these drugs were associated with reduced pain scores. Higher DE doses were associated with worse mood (depression and pain anxiety), functioning (total, physical and

psychosocial) and less acceptance of pain and other emotions. However, higher DE dose was not associated with experiencing less success in pursuing valued goals.

Results for ME were less consistent, but in general higher doses remained associated with worse functioning. Poorer total and physical functioning was correlated with higher ME dose. Higher ME was also associated with poorer psychosocial functioning and less success in pursuing valued goals. However, there was no association between pain acceptance, general acceptance, pain anxiety and depression and ME dose.

********** **TABLE 3 ABOUT HERE, PLEASE** **********

Potential confounding variables – multivariate analysis

The association between DE, ME and mood / functioning variables was clear, but it was also possible that this might be accounted for by a third, confounding variable. It could be argued that perhaps older patients, or those in more pain, might have both greater disability and higher medication prescription, in which case, age or pain would account for the relationships seen. We decided to examine the impact of (1) demographic and (2) condition-related variables on our results. We selected two dependent variables, which were both clinically important and also most closely associated with our medication variables – that is, Depression and Total Disability.

We examined the correlations between these dependent variables and five potential confounders, that is, (1) age, (2) gender, (3) duration of pain, (4) pain intensity and (5) number of doctors seen for pain. Age and Pain Intensity were correlated with Total Disability; Pain Intensity was correlated with Depression (all $p < .05$) . Thus, we entered these potential confounding variables in the first step of a series of hierarchical regression

equations, as seen in Table 4. (There was no analysis for Depression and ME dose, as they were not correlated.) In each case, the medication variable in the second step of the equation accounted for a significant amount of variance in the dependent variable (R^2, all $p < 0.01$), after the potential confounder had been controlled out. Thus, the associations between medication dose and Depression / Disability cannot be fully accounted for by potentially confounding demographic variables, or by the influence of pain intensity.

********** TABLE 4 ABOUT HERE, PLEASE **********

Examination of different dose ranges

Concern has been raised about high opioid doses; thus, it may be that higher opioid doses are specifically associated with more severe impairment. To investigate this, we divided the data by median split of ME dose, examining the 50% of patients with higher doses (i.e. those with daily doses of between 48mg and 749mg, N = 114). We repeated the correlations in Table 1, and found that associations were not stronger; only correlations with physical disability and total disability remained significant ($p < .05$). We then explored the possibility that being on opioids at all might be harmful. We created a dichotomous variable (on opioids, at any dose, or not) and repeated the correlations in Table 3; being on opioids at any dose was associated with greater physical, psychosocial and total disability ($p < .01$) and less valued living success ($p < .05$).

Most participants were not taking Benzodiazepines (69.7%). In the analysis above, we examined the whole range of doses (including zero). Here, we selected only those who were taking these drugs (N = 67) and examined associations between their DE dose and functioning / distress. Obviously, there is a substantial loss in statistical power to detect differences between N = 229, and N = 67. However, higher DE remained associated with

higher pain related fear and total disability ($p < .05$). Notably, in those taking benzodiazepines, correlations between dosage and unwillingness to accept pain or emotions were significant (pain acceptance ρ -.33 $p < .05$, general acceptance, ρ -.39 $p < .01$).

Opioids and benzodiazepines singly and in combination

We wished to examine the effect of combined benzodiazepine and opioid prescription; however the distributions of ME and DE were so skewed that it was not appropriate to generate an interaction variable by multiplication. Instead, we examined the impact of taking a given class of drug, irrespective of dose. We looked a participants who were taking (1) neither class of drug, (2) opioids only, or (3) both opioids and benzodiazepines (only four patients were on a benzodiazepine but no opioid). Results can be seen in Figures 3 – 5. There were significant differences between the groups on all three variables (One-way ANOVA, all $p < .01$). Post hoc testing using Tukey's HSD showed that being on both drugs was worse than just being on opioids alone for depression and pain anxiety (both $p < .01$), but not for total disability. Opioids alone were associated with higher levels of total disability, but being on the combination was not significantly more disabling than opioids alone ($p > 0.05$).

********** FIGURES 3 to 5 ABOUT HERE, PLEASE **********

Discussion

In a sample of patients with severe, long-standing chronic pain attending a specialist service, opioid and benzodiazepine / Z-drug prescription was common. For each patient, we examined their various opioid medications and converted these into a single daily Morphine

Equivalent (ME) dose, repeating the process to create a Diazepam Equivalent (DE) dose from benzodiazepines and Z-drugs. Higher ME and DE doses were not associated with better functioning or reduced distress on any measure; this finding for ME echoed previous findings on opioid dose[6,7]. The pattern of results for benzodiazepines was clear. Higher DE doses were associated with worse outcomes in most domains, whereas higher ME doses were more specifically associated with higher disability. The relationships seen were not fully accounted for by confounding variables such as pain intensity or age. There was evidence that being on both opioids and benzodiazepines was worse than being on opioids alone for mood variables. Higher doses of these drugs were not associated with lower pain. This adds to previous literature that has focused on the medical effects of these drugs and on addiction; it is the first direct contrast of opioid and benzodiazepine use in a chronic pain sample.

Guidance and commentary around opioid prescription have been common in the recent pain literature. Recommendations to avoid high opioid doses have been endorsed by professional bodies, whereas benzodiazepine prescription has not attracted comment. The results in this study suggest that this emphasis requires revision. Although less than a third of patients were taking benzodiazepines, the associations between this class of drug and poor outcomes was more consistent than for opioids. Also, increasing doses in the higher dose range (top 50% of our sample) – targeted for disapproval in recent guidance – were not more closely or consistently associated with poor outcome. Rather, in our sample, being on an opioid at all was associated with worse physical functioning and less success in leading a valued life.

Thus, the results for opioid doses were not as anticipated. In our sample, most were taking either no opioid, or doses in the 'approved' range of <120mg (73%). We examined the 50%

of participants with the highest ME doses (49mg to 749mg), expecting increased dose in this range to be more closely associated with inability to accept pain, pain-associated fear and other poor outcomes. This was not the case, although higher doses remained associated with poorer physical functioning. Previous studies have, in contrast, found specific effects for the higher dose ranges[6,7]. It may be that patient characteristics, or length of prescription, can account for the difference. The patients in the current study had long-standing difficulties and were at a highly specialist service; whilst neither of the contrasting studies report disease duration, Kobus et al.[6] sampled from primary care, so would probably have included more patients with lower disease duration and less lengthy opioid prescription. Also, it is not possible to contrast the mean absolute doses levels in our study and previous research (means are not obtainable from those papers) and neither we nor previous authors have captured duration of opioid consumption. It is possible that our patients were taking lower absolute doses than those seen in the previous, US-based, studies, or that they had been taking opioids for longer, resulting in the development of tolerance.

In contrast, the effects of benzodiazepines were worse than anticipated. As for opioids, DE dose was associated with worse total disability and physical disability. However, there was also a clear emotional association, with worse depression and pain related fear, and higher doses associated with a poorer ability to accept emotions, or pain in general. As noted above, we had no data on how long participants had been taking these drugs. However, we had no reason to believe that any prescriptions were short term, and it seems unlikely that we coincidentally assessed nearly a third of the sample at a time that they were on a short term prescription. Previous studies have also reported a surprisingly high level of benzodiazepine prescription in patients on high doses of opioids (e.g. 32%[5], compared to 37% in this study).

Negative medication effects in severe chronic pain

The negative effects of long-term benzodiazepine use are so well documented that our results are not surprising. There is no positive evidence for the use of benzodiazepines in any area of long-term chronic pain, yet nearly a third of our participants were taking them, and were in a worse state than those without these medications. Increasing benzodiazepine dose was seen in patients with the least ability to tolerate pain or negative emotions. Thus, these data echo other studies which found that benzodiazepine use was most common in the most distressed patients, and in those patients least likely to be able to be discontinue these drugs. Of course, benzodiazepines have negative effects on those without pain; however, they may also specifically impact areas where patients with chronic pain already struggle. For example, people with chronic pain regularly report difficulties with cognitive function[26,27], and cognitive function is likely to be further worsened by long-term benzodiazepine use. The benzodiazepine doses seen in this study were not particularly large; thus, it is noteworthy that objectively moderate doses were associated with poorer mood and functioning.

The associations found in this study do not prove causation. It can be argued that, for example, it is those patients with highest levels of pain-related fear, or difficulty accepting emotions, who end up taking these medications in the long term. Also, it might be argued that although patients who were taking opioids or benzodiazepines were worse off, the drugs were in fact protective and the patients might have been worse without them. The latter argument is speculative and is contradicted by other data; Murphy et al.[28] examined opioid cessation in the context of pain rehabilitation and showed no negative impact of stopping these drugs. The former argument about causation is undeniable, and only studies that manipulate drug dose (for example, drug cessation studies) can establish causation. However, data from this study show no benefit of taking any of these medications at any dose range, and many negative associations. Thus, it is the responsibility of those who

support the prescription of these agents, particularly benzodiazepines, to show any evidence for their positive effects in long term chronic pain. Also, the causal role of opioids and benzodiazepines in iatrogenic harm is not in dispute in other areas of the literature. For example, the causal role of benzodiazepines in cognitive impairment and fatal opioid overdose is clear [10, 29].

Finally, the associations seen in this study were fairly small and there are many potential confounding variables that we did not examine. Whilst it is reassuring that opioids and benzodiazepines were not strongly and absolutely associated with decrements in wellbeing, they were overall associated with negative outcomes in a patient population already struggling with a severe pain condition and associated disability and low mood.

There are other limitations to this study. Morphine- and diazepam-equivalent values are controversial, and the specific conversion values that we used can be challenged. However, any alternative conversion value would also be far from definitive, and we do not believe that any minor changes to the multipliers used would make a substantive difference to our results. With hindsight, it is also a weakness that we did not know how long participants had been using their drugs for, or why (in the case of benzodiazepines) they had been prescribed. It seems possible that the worst sedating effects of these drugs may occur early in their use, and that having recorded 'duration of use' might allow us to explore the potential role of tolerance in our results. We also focused on overall dose, where future studies may explore differences between, for example, immediate release and sustained release opioid preparations.

These results have implications for clinical practice and guidance. On the basis of these results and broader evidence[10], it seems difficult to justify the long-term prescription of

benzodiazepines in long-standing chronic pain. No evidence supports this, and our results argue that it may be harmful. This replicates decades of work in other fields associating long-term benzodiazepine use with negative outcomes, and specifically with cognitive impairment. For most uses of benzodiazepines, for example as anxiolytics, hypnotics, or muscle relaxants, only short term use is indicated. Long term benzodiazepine prescription may be actively harmful[10,29]. It may be appropriate for prescribers in the pain field to be more aware of the large literature on the negative effects of longer-term use and on the clear role of benzodiazepines in unintentional opioid overdose[10,13,29].

Our results also suggest that the focus of opioid guidance might be broadened. National and international guidance has focused on overall opioid load, recommending maximum safe or evidence supported levels. This remains important, as we found that increasing dose at all ranges was associated with increased physical disability. However, the intuitive clinical picture of a patient sedated and struggling to function on a high opioid dose was not fully borne out by our results, in contrast to previous research. High doses may certainly be associated with medical side effects, but we found that there were no necessary associations between a high opioid load (the top 50% of ME doses in our sample) and psychosocial disability, depression, or living a valued life. Dosage alone may not be the most fruitful way to understand the impact of opioids. Future research and guidance may focus on other issues, such as examining duration of opioid use, the impact of immediate release versus sustained release opioids, and the combination of opioids with benzodiazepines.

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Author Contributions

JGG had the idea for the study, led on writing the paper and bears overall responsibility for the data. PB provided expert commentary on methodological and clinical aspects of medication issues. DG wrote sections of the paper and contributed to data analysis. All authors discussed the results and contributed to the manuscript.

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Figure Legends

Figure 1: Morphine-Equivalent Dose

Figure 2: Diazepam-Equivalent dose

Figure 3: Depression scores of different drug combinations

Figure 4: Disability scores for different drug combinations

Figure 5: Pain Anxiety scores for different drug combinations