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| **Table S1: Kolmogorov-Smirnov (KS test) Analysis of Normality and Bartlett’s Test for Homogeneity of Variance and Mean vs. Median for Guinea Pig Data Sets a** |
| **Test Groups**  | Mean  | SD | Median  | KS TestP<0.10  | Bartlett Test P<0.10 | Parametric Properties b  |
|  |  |  |  |  |  |  |
| **Peak Response Latency (Day 0) (Figure 1A-D)**  |  |  |  |  | NS | Yes |
| IT NaCl | 9.4 | 1.1 | 9.1 | NS |  |  |
| IT Morphine  | 10.6 | 0.9 | 10.8 | NS |  |  |
| IT DMT DALDA | 9.2 | 0.8 | 8.4 | NS |  |  |
| ITPZM21 | 10.4 | 0.9 | 9.4 | NS |  |  |
| **Peak Response Latency (Day 3) (Figure 1A-D)**  |  |  |  |  | NS | Yes |
| IT NaCl | 9.7 | 1.7 | 9.3 | NS |  |  |
| IT Morphine  | 17.1 | 3.2 | 19.1 | NS |  |  |
| IT DMT DALDA | 17.4 | 2.6 | 18.0 | NS |  |  |
| ITPZM21 | 17.2 | 2.3 | 17.4 | NS |  |  |
| **AUC Analysis:** AUC (days 0-7)  **(Figure 1E)**  |  |  |  |  | NS | Yes |
| IT NaCl  | 6.3 | 93 | 22.0 | NS |  |  |
| IT Morphine  | 246 | 162 | 276 | NS |  |  |
| IT DMT-DALDA | 312 | 85 | 312 | NS |  |  |
| IT PZM21 | 264 | 134 | 323 | NS |  |  |
|  |  |  |  |  |  |  |
| **LAD2 Degranulation (Figure 5)** |  |  |  |  | NS  | Yes c  |
| Morphine (10 µM) | 0.478 | 0.028 | 0.475 | ND c |  |  |
| Morphine (1 µM) | 0.343 | 0.030 | 0.340 | ND c |  |  |
| Morphine (0.1 µM) | 0.323 | 0.005 | 0.320 | ND c |  |  |
| PZM21 (10 µM)  | 0.293 | 0.022 | 0.290 | ND a |  |  |
| PZM21 (1 µM)  | 0.283 | 0.040 | 0.280 | ND c |  |  |
| PZM21 (0.1 µM)  | 0.273 | 0.040 | 0.270 | ND a |  |  |
| DMT-DALDA (10 µM) | 0.335 | 0.024 | 0.335 | ND a |  |  |
| DMT-DALDA (1 µM) | 0.298 | 0.022 | 0.290 | ND c |  |  |
| DMT-DALDA (0.1 µM) | 0.293 | 0.013 | 0.290 | ND c |  |  |
| PBS | 0.253 | 0.021 | 0.250 | ND c |  |  |
|  |  |  |  |  |  |  |
| **Fibroblast Proliferation (Figure 6A)**  |  |  |  |  | SIG  | No  |
| Buffer | 15.9 | 2.6 | 16.8 | SIG  |  |  |
| Morphine (0.0003)  | 18.4 | 3.3 | 17.5 | NS |  |  |
| Morphine (0.003)  | 18.8 | 3.0 | 17.5 | NS |  |  |
| Morphine (0.03)  | 16.9 | 4.4 | 17. | NS |  |  |
| Morphine 0.3  | 17.7 | 6.3 | 17.8 | NS |  |  |
| Morphine (3)  | 24. | 3.4 | 23.8 | NS |  |  |
| Morphine (30)  | 22. | 2.4 | 21.8 | SIG  |  |  |
| Morphine (300) | 11.4 | 1.6 | 11.5 | NS |  |  |
|  |  |  |  |  |  |  |
|

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| --- | --- | --- | --- | --- | --- | --- |
| **Fentanyl (Figure 6B)**  |  |  |  |  |  | ANOVA  |

 |  |  |  |  | NS  | No  |
| Control | 7.42 | 0.585 | 7.50 | NS |  |  |
| Fentanyl (0.0000003) | 7.58 | 1.800 | 7.50 | NS |  |  |
| Fentanyl (0.000003) | 8.25 | 1.640 | 8.00 | NS |  |  |
| Fentanyl (0.00003) | 9.00 | 2.020 | 8.25 | SIG |  |  |
| Fentanyl (0.0003) | 7.92 | 2.040 | 7.25 | NS |  |  |
| Fentanyl (0.003) | 8.25 | 1.860 | 8.00 | NS |  |  |
| Fentanyl (0.03) | 7.42 | 2.220 | 6.25 | NS |  |  |
| Fentanyl (0.3) | 7.17 | 1.440 | 6.75 | NS  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **PZM21 (Figure 6C)** |  |  |  |  | NS | Yes |
| Control | 22.9 | 3.15 | 22.8 | NS |  |  |
| PZM 21 0.03 | 20.8 | 2.99 | 19.8 | NS  |  |  |
| PZM 21 0.3 | 21.1 | 4.04 | 20.3 | NS |  |  |
| PZM 21 3 | 20.1 | 3.12 | 21.0 | NS |  |  |
| PZM 21 30 | 21.5 | 3.59 | 21.8 | NS |  |  |
| Morphine  | 30.6 | 3.83 | 31.0 | NS  |  |  |
|  |  |  |  |  |  |  |
| **DMT DALDA (Figure 6D)**  |  |  |  |  | NS  | No  |
| Control | 24.5 | 3.39 | 23.8 | NS |  |  |
| Morphine | 32.2 | 3.13 | 32.5 | NS |  |  |
| DMT DALDA 0.0003 | 27.0 | 3.15 | 27.5 | SIG |  |  |
| DMT DALDA 0.003 | 25.3 | 4.24 | 24.3 | NS |  |  |
| DMT DALDA 0.03 | 24.3 | 2.46 | 24.3 | NS |  |  |
| DMT DALDA 0.3 | 22.4 | 2.20 | 21.8 | NS |  |  |
| DMT DALDA 3 | 24.5 | 3.39 | 23.8 | NS |  |  |
| DMT DALDA 30 | 32.2 | 3.13 | 32.5 | NS  |  |  |
|  |  |  |  |  |  |  |
| **Fibroblast Proliferation (Figure 6E)**  |  |  |  |  | NS | Yes |
| Control  | 18. | 2.0 | 18. | NS |  |  |
| Morphine  | 25. | 4.2 | 25. | NS  |  |  |
| Morphine + Naloxone | 24. | 4.7 | 24. | NS  |  |  |
|  |  |  |  |  |  |  |
| **Fibroblast Proliferation (Figure 6F)**  |  |  |  |  |  | No |
| Buffer | 15.9 | 2.2  | 15.8 | NS  |  |  |
| Cromolyn | 15.6 | 1.1 | 15.8 | NS |  |  |
| Morphine | 21.1 | 2.7 | 18.9 | NS |  |  |
| Morphine + Cromolyn | 18.1  | 1.5 | 18.5 | NS  |  |  |
|  |  |  |  |  |  |  |
| **Fibroblast Collagen (Figure 7)** |  |  |  |  | NS | Yes |
| Buffer | 1.01 | 0.029 | 1.01 | NS |  |  |
| Morphine | 1.20 | 0.074 | 1.17 | NS |  |  |
| DALDA  | 1.06 | 0.044 | 1.05 | NS  |  |  |
| PZM21 | 0.90 | 0.058 | 0.87 | NS |  |  |
|  |  |  |  |  |  |  |
| **AUC Analysis (Figure S1)** |  |  |  |  | NS | Yes |
| IT Sal  | 30 | 113 | 40 | NS |  |  |
| ITMS + Nal  | 21 | 113 | -20 | NS |  |  |
| IT MS + Sal  | 236 | 206 | 260 | NS |  |  |
|  |  |  |  |  |  |  |
| **Fibroblast Migration (Figure S2)** |  |  |  |  | NS | No  |
| Control | -28.5 | 53.4 | -32.5 | NS |  |  |
| MS (0.2) alone | 21.1 | 32.6 | 28.0 | NS |  |  |
| MS (2.0)  | 87.0 | 44.3 | 74.2 | NS |  |  |
| MS (20)  | 102.0 | 77.9 | 94.7 | NS |  |  |
| MS (2) + Nal (2) | 98.6 | 81.0 | 74.0 | SIG |  |  |
| MS (2) + Nal (20) | 79.7 | 35.6 | 79.4 | NS |  |  |
|  |  |  |  |  |  |  |
| 1. Calculated with GraphPad Prism, 6 (6.0h, 2015)
2. Parametric criteria are similarity of means/medians for any given group; similarity of SD by inspection across treatment groups; nonsignificance (NS) of Kolmogorov-Smirnov (KS test) analysis of normality and nonsignificance (NS) of Bartlett’s test for homogeneity of variance (e.g. failure to reject the hypothesis of normality and homogeneity of variance.
3. Group size too small to calculate Kolmogorov-Smirnov. Parametric analysis selected based on homogeneity of variance and congruity of group means and medians
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