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ANTI-NOCICEPTIVE EFFECTS OF ANTIDEPRESSANT AND ANTICONVULSANT DRUGS IN THE TREATMENT OF ACUTE PAIN IN MICE

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ABSTRACT

Chronic use of non-steroidalanti-inflammatory drugs (NSAIDs) and opioids are associated with gastric ulceration and drug dependence respectively. In previous studies some antidepressants and anticonvulsants showed clinical effectiveness in the treatment of neuropathic and chronic pain. However, no scientific evidence is available showing effectiveness of antidepressants and anticonvulsant drugs in acute pain. In some cases, where patients are at risk of NSAIDs or opioid associated adverse effects, acute pain is difficult to manage by these agents. Therefore, the purpose of current study was to compare the analgesic effects of specific serotonin reuptake inhibitor (SSRI), specific norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressents (TCA) and anticonvulsant drug lamotrigine. Animals were divided in groups (n=5). Control animals were administered water, positive control group was treated with paracetamol or ibuprofen. Visceral pain was induced by intra peritoneal (IP) injection of 2% acetic-acid or two phasic pain was induced (central and peripheral pain) by5% formalin IP and thermal stimuli like hot plate test (central sensitization) for the assessment of analgesic effects in mice. Results showed that citalopram, duloxetine, amitriptyline, fluvoxamine and lamotrigine were effective in reducing pain significantly in all test groups and analgesic effectiveness was comparable with positive control. In conclusion, citalopram, duloxetine, amitriptyline, fluvoxamine and lamotrigine possess significant potential to produce analgesia in acute nociceptive pain, and may be used as analgesic in acute pain conditions where NSAIDs treatments are not recommended.

INTRODUCTION

Pain is an unpleasant emotional or sensory experience (physical or physiological responses) to tissue damage or injury (Steeds, 2013). It is not only unpleasant sensation but also an essential indicator to find remedy for survival. It is a complex sensory modality and difficult to define quantitatively (Sandeep, 2011). Pain during disease condition is different from normal pain because external stimulus is absent in disease state so pains are classified according to pathogenesis (Schaible, 2007). Acute pain lasts not more than three months and is self-limiting (Pengel, Maher and Refshauge, 2002).

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In contrast chronic pain lasts more than 6 months (Russo, 1998). The therapy of acute pain is aimed at treating the underlying cause and interrupting the nociceptive signals (Grichnik & Ferrante, 1991). Visceral pain described as a pain when internal organs are damaged and injured. They respond to mechanical and chemical stimuli that induced pain such as burn or cutting (Urch *et al*., 2008). Nociceptors are sensory receptors and have specialized nerve cell endings that perceive pain sensation (Sandkühler, 2009). Afferent impulses travel from peripheral tissue to spinal cord via two types of nerve fibers: A-fiber and C-fiber (Schofield *et al*., 2002). In current medical practice peripheral pain is treated with NSAIDs while central pain is treated by using opiate analgesics, anesthetics, antidepressants and anticonvulsants. Antidepressants and anticonvulsants influence the motivational aspect of pain and would have effect on higher centers in brain (Marchand,

2008). More than 40 double blind, placebo-controlled trials showed that antidepressants had important role in controlling headache, rheumatic pain, central pain, peripheral pain, chronic and cancer pain of different etiologies (Jann and Slade, 2007). It has been hypothesized that pain and depression share same biochemical mechanism of action because depression is frequently observed in chronic pain patients (Mico *et al*., 2006). In general, drugs having serotonergic and noradrenergic mechanisms are more efficient analgesics, even though exact mechanisms remain poorly understood (Cobo-Realpe *et al*., 2012). Mice deficient in serotonin and norepinephrine transporters showed increased pain sensitivity in allodynia. These studies provide pharmacological evidences of antidepressant's efficacy in pain (Jann and Slade, 2007). Similarly, antiepileptic drug lamotrigine produced slight inhibition of tactile allodynia in rat but only at very high dose. Clinically lamotrigine is also widely and effectively used for the management of neuropathic pain (Fox *et al*., 2003). Although, NSAIDs and opioids are effective in the management of acute and chronic pain respectively, however their long-term uses are also associated with gastric ulceration and drug dependence. In present study we focused to determine the analgesic effect of antidepressant and anticonvulsant drugs in management of acute pain. Paracetamol and ibuprofen were used as reference drugs.

MATERIALS AND METHODS

ANIMALS

Swiss albino male mice 20-30g were obtained from animal house of The University of Lahore. Animals were maintained at 22±2 ^{0}C with controlled humidity. They were maintained on a 12h day and night cycle. Food and water were provided ad libitum. Food was withdrawn 12 hours before experimentation.

CHEMICALS

Acetic acid (Sigma), NaCl (Sigma), Formalin (Sigma) were purchase from local market where as Ibuprofen, Paracetamol (PCM), Amitriptyline (AMT), Fluvoxamine (FLX) and Citalopram (CTP), were kindly gifted by Unison Chemical Raiwind road Lahore-Pakistan. Duloxetine (DLX) and Lamotrigine (LTG) were received as gift from High Noon Laboratories, Lahore-Pakistan.

ACUTE PAIN MODELS

ACETIC ACID INDUCED WRITHING TEST

Long lasting visceral pain was produced by intra-peritoneal injection of dilute acetic acid and response to this stimulus measured by observing the number of writhes (Fox *et al*., 2003; Gawade, 2012). Briefly, mice were divided into 7 groups (5 mice per group); group 1: control, group 2: ibuprofen (80mg/kg), group 3: CTP (3mg/kg), group 4: DXT (25mg/kg), group 5: AMT (15mg/kg), group 6: FLX (35mg/kg), group 7: LTG (20mg/kg). All the drugs were administered orally by feeding tube. Control group was given normal saline. One hour post treatment, all the groups were injected (10ml/kg) of 2% acetic acid intra-peritoneal. Number of writhing moments consisting of contraction of abdominal muscles leading to extension of hind limb and periodic arching of body were counted for 20min at 5min interval, using hand tally counter. The degree of analgesia was calculated by using the formula of percentage effectiveness.

% Effectiveness = (Number of writhes in control – Number of writhes in treated/Number of writhes in control) × 100

FORMALIN TEST

Assessment of formalin induced pain was assessed by monitoring the licking and paw lifting behavior as described before (Munro, 2009). Animals were divided in groups as mentioned above and assigned different doses. Briefly, mice were divided into 7 groups (5 mice per group); group 1: control, group 2: PCM (400mg/kg), group 3: CTP (35mg/kg), group 4: DXT (15mg/kg), group 5: AMT (30mg/kg), group 6: FLX (40mg/kg), group 7: LTG (70mg/kg). All the doses were administered orally and control group was given normal saline accordingly. One hour after administration of different drugs, animals were injected 50µl of 5% formalin solution in the dorsal surface of hind paw using fine needle. Mice were observed for the number of counts of paw licking and paw-lifting during first phase (0-5 min) and second phase (15-45 min). Percentage effectiveness was calculated by using the formula.

% Effectiveness= (Value of control –value of test drug /value of control) × 100

HOT PLATE TEST

The analgesic activity of the test drugs was also assessed by measuring the latency time in response to heat stimulus as described earlier (Eddy and Leimbach, 1953). Briefly, mice were divided into 7 groups, each group consisting of 5 mice. Group 1: control, group 2: Paracetamol (PCM) (400mg/kg), group 3: CTP (20mg/kg), group 4: DXT (20mg/kg), group 5: AMT (20mg/kg), group 6: FLX (15mg/kg), group 7: LTG (30mg/kg).All the drugs were administered orally and control group was given normal saline by using feeding tube. The animals were placed on hot plate (53± 0.2℃) at 0, 30, 60 and 90 minutes following the oral administration of drugs. The time (Latency time) until animal started either licking or jumping was recorded. Maximum latency of 60 seconds was used in order to avoid tissue damage to the animals. When reaction time reached more than 60 seconds, it was regarded as reaction time 60seconds. Percentage of maximum possible effects (MPE) is determined by following formula:

% MPE= (Post drug latency-Pre drug latency / Cut off time-Pre drug latency) × 100

STATISTICAL ANALYSIS

Data were recorded as MEAN±SEM. One way ANOVA was used to determine statistical significance between groups. A value of $p<0.05$ was considered significant. All statistical analysis was done using SPSS.

RESULTS

The effects of different categories of drugs on acetic acid-induced writhing and paw-licking behavior are presented in

Table 1. Ibuprofen 80mg/kg completely abolished nociceptive effect of acetic acid in both writhing and licking behavior (100%). CTP 3mg/kg orally showed somewhat fluctuating type of decrease in both behaviors. Maximum effect was observed at 15 to 20 minutes in writhing whereas paw-licking was protected maximally (90.91%) at 10 to 15 minutes. DXT 25mg/kg exhibited 100% protection at 5 minutes and declined to 72.2% at 20 minutes in writhing whereas in paw-licking the complete protection was observed at 15 to 20 minutes. AMT 15mg/kg orally provided significant decrease in writhing and paw protection. The protection against writhing declined with time whereas against licking behavior increased with time. FLX 35mg/kg also showed same trend as of AMT.

The anticonvulsant agent LTG 20mg/kg showed maximum (94.12%) decrease in writhing, the effect diminished to 66.6% at 15 to 20 minutes interval. Contrary to this, protection against paw-licking showed time dependent trend meaning by minimum (50%) at 5 minutes and 94.44% at 15 to 20 minutes. Table 2 presents the effect of different oral doses of antidepressants and anticonvulsant on formalin induced paw-licking and paw-lifting behavior. PCM 400mg/kg completely protected (100%) second phase (15-45 minutes) of licking and paw-lifting but in first phase (0-5 minutes) almost no protection was observed in both paw-licking and paw-lifting. CTP 35mg/kg caused protection against paw licking that reached maximum level (87%) with time at 31 to 45 minutes.

Table 1. Effect of different drugs on acetic acid induced writhing and paw-licking behavior in mice

Test Drugs	Writhing				Paw-Licking			
	0-5 (min)	5-10 (min)	10-15 (min)	15-20 (min)	0-5 (min)	5-10 (min)	10-15 (min)	15-20 (min)
Control	6.8 ± 0.63	5.2 ± 0.97	6.6 ± 0.4	7.2 ± 0.917	6.8 ± 0.37	5.2 ± 0.97	6.6 ± 0.4	7.2 ± 0.917
IBO 80(mg/kg)	0 ± 0 (100.00)	0 ± 0 (100.00)	0 ± 0 (100.00)	0 ± 0 (100.00)	0 ± 0 (100.00)	0 ± 0 (100.00)	0 ± 0 (100.00)	0 ± 0 (100.00)
CTP 3(mg/kg)	0.4 ± 0.24* (94.12)	0.2 ± 0.2* (96.15)	1 ± 0.316* (84.85)	0.4 ± 0.24* (94.44)	2.6 ± 0.4 (61.76)	2.2 ± 0.2* (57.69)	0.6 ± 0.4* (90.91)	1.6 ± 0.6* (77.78)
DXT 25(mg/kg)	0 ± 0 (100.00)	0.4 ± 0.4 (92.31)	2 ± 0* (69.70)	2 ± 0.548* (72.22)	0.6 ± 0.6* (91.18)	2.6 ± 1.939 (50.00)	1.6 ± 1.2 (75.76)	0 ± 0 (100.00)
AMT 15(mg/kg)	0.6 ± 0.6* (91.18)	1.2 ± 0.7* (76.92)	1.6 ± 0.5* (75.76)	0.8 ± 0.3* (88.89)	1.8 ± 0.9* (73.53)	1 ± 0.7* (80.77)	1.2 ± 0.4* (81.82)	0.2 ± 0.2* (97.22)
FLX 35(mg/kg)	0 ± 0* (100.00)	0.6 ± 0.4* (88.46)	0.8 ± 0.2* (87.88)	1.6 ± 0.4* (77.78)	2.8 ± 0.9* (58.82)	0 ± 0* (100.00)	0.8 ± 0.8* (87.88)	0.8 ± 0.49 (88.89)
LTG 20(mg/kg)	0.4 ± 0.245* (94.12)	1.4 ± 0.6* (73.08)	1.8 ± 0.583* (72.73)	2.4 ± 0.51* (66.67)	3.4 ± 0.812 (50.00)	2.2 ± 0.6 (57.69)	1 ± 0.4 (84.85)	0.4 ± 0.245 (94.44)

Results are expressed as Mean ± SEM, N=5. * P<0.05, as compared to control value. Percent effectiveness values are presented in parentheses with respect to control.

Table 2. Effect of different drugs on formalin induced paw-licking and paw-lifting behavior in mice

Test Drugs	Licking			Paw Lifting		
	0-5 (min)	15-30(min)	31-45(min)	0-5(min)	15-30(min)	31-45(min)
Control	10.4 ± 0.67	4.4 ± 0.51	7.8 ± 0.58	2.4 ± 0.54	1.8 ± 0.2	1.2 ± 0.2
PCM 400(mg/kg)	8.4 ± 0.67 (19.23)	0 ± 0 (100.00)	0 ± 0 (100.00)	4.6 ± 0.927 (-91.66)	0 ± 0 (100.00)	0 ± 0 (100.00)
CTP 35(mg/kg)	3.6 ± 0.5* (65.38)	0.6 ±0.2 (86.36)	1 ± 0* (87.18)	1 ± 0.316 (58.33)	0 ± 0* (100.00)	0 ± 0* (100.00)
DXT 15(mg/kg)	1 ± 0.3* (90.38)	0.8 ± 0.2* (81.82)	1.6 ± 0.4* (79.49)	0.4 ± 0.2* (83.33)	0.2 ± 0.2* (88.89)	0.2 ± 0.2 (83.33)
AMT 30(mg/kg)	0.8 ± 0.3* (92.31)	0.2 ± 0.2* (95.45)	1.2 ± 0.2* (84.62)	0.2 ± 0.2 (91.67)	0 ± 0* (100.00)	0.8 ± 0.2* (33.33)
FLX 40(mg/kg)	3 ± 0.44* (71.15)	0.2 ± 0.2 (95.45)	0 ± 0* (100.00)	1 ± 0.447 (58.33)	0 ± 0* (100.00)	0 ± 0* (100.00)
LTG 70(mg/kg)	3.2 ± 0.3* (69.23)	1 ± 0.316* (77.27)	1.2 ± 0.2 (84.62)	0.8 ± 0.5 (66.67)	0 ± 0 (100.00)	0.6 ± 0.2 (50.00)

Data are represented as MEAN±SEM (n=5) *p<0.05 significant as compared to control group. The figures written in parentheses represent percent effectiveness values with respect to control.

Table 3. Effect of different drugs on latency time to hot plate induced paw-lifting or jumping behavior in mice

Test Drugs	Latency time		
	30 (min)	60 (min)	90 (min)
Control	11.2 ± 0.7	10.8 ± 0.37	11 ± 0.447
PCM 400(mg/kg)	30.2 ± 0.37 (62.91)	33.8 ± 1.06 (68.05)	39.4 ± 2.65 (72.08)
CTP 20(mg/kg)	41.8 ± 1.068* (73.21)	40.2 ± 1.35* (73.13)	40.2 ± 1.356* (72.64)
DXT 20(mg/kg)	36 ± 1.2* (68.89)	36.6 ± 1.7* (70.49)	33 ± 1.5* (66.67)
AMT 20(mg/kg)	34.8 ± 2.35* (67.82)	35 ± 2.55* (69.14)	37 ± 1.393* (70.27)
FLX (15mg/kg)	39 ± 1.208* (71.28)	40.1 ± 2.34* (73.07)	40.6 ± 1.96* (72.91)
LTG 30(mg/kg)	27.8 ± 0.37* (59.71)	30.4 ± 0.927* (64.47)	36.4 ± 1.077* (69.78)

Data are represented as MEAN±SEM n=5, *P<0.05 significant as compared to control group. The figures written in parentheses represent percent maximum possible effect (% MPE) values with respect to control.

In the same way paw-lifting behavior was completely abolished (100%) at 15 to 45 minutes. DXT 15mg/kg exhibited decreasing trend with time in case of paw-licking, declining from 90 to 79% whereas same trend was observed in paw-lifting behavior at 15 to 45 minutes. AMT 30mg/kg showed same trend as DXT in both paw-licking and paw-lifting. Maximally 84% protection was observed in licking behavior whereas paw-lifting behavior drastically decreased from 100% to 33% at 31 to 45 minutes. FLX 40mg/kg showed increasing effect with time in both paw-licking and paw-lifting behaviors. Anticonvulsant drug, lamotrigine 70mg/kg orally provided increasing response of protection in paw-licking (84%) at 0 to 45 minutes whereas decreased effectiveness in paw lifting at 15 to 45 minutes (50%).The effect of different drugs on latency in hot plate test is presented in Table 3. PCM 400mg/kg showed increase in latent period to respond to thermal stimulus, maximum increase observed (72%) at 90 minutes. CTP 20mg/kg exhibited almost same results throughout the experiment from 30 to 90 minutes (73% increases in latency time). DXT 20mg/kg showed maximum effect at60 minutes (70%). AMT 20mg/kg showed same increasing trend of effectiveness like PCM, maximum effect was observed (70%) at 90minutes. FLX 15mg/kg followed almost same trend of protection against thermal stimuli like CTP. LTG 30mg/kg was found to provide time-dependent protection against nociceptive pain induced by thermal stimulus, the maximum effect of 69.7% achieved at 90 minutes post dosing.

DISCUSSION

For the management of some chronic neuropathic pains, NSAIDs have been proved less efficacious. Combinations of NSAIDs with adjuncts antidepressants/anticonvulsant have more beneficial effect in the management of neuropathic pain but limited studies are available to support this idea vigorously. Present study focuses on effectiveness of orally administered clinically used antidepressants and anticonvulsants on different acute pain models of mice in which chemical and thermal stimuli were employed to induce pain. The tricyclic antidepressant amitriptyline showed test dependent anti-nociceptive effects, the most potent effect observed in pain induced by chemical stimuli. Amitriptyline showed maximum effectiveness in acetic acid induced pain responses (writhing and paw-licking). Our results are in agreement with earlier observations.

According to Mico *et al*., 2006 test dependency of anti-nociceptive effects of amitriptyline is repeatedly found and chemical test appeared to be most sensitive. Similarly, Valverderk*et.al* demonstrated that TCAs expressed much more effective anti-nociceptive activity in the formalin test than electric stimulus test (Valverderk *et al*., 1994). The reasons for differences in the sensitivity of animals' models are not clear. The test dependency of amitriptyline most probably reflects differential involvement of centrally and peripherally located mechanisms. Recent studies showed that anti-nociceptive effect of amitriptyline is mediated via active metabolites which selectively increase norepinephrine reuptake (Sindrup *et al*., 2005).In formalin test amitriptyline inhibited both phase 1 and phase 2 licking and paw-lifting behaviors. Various studies about amitriptyline effectiveness in formalin induced licking and flinching behavior also supported the present data (Sawynok and Reid, 2001; Acton *et al*., 1992). In phase 2, an elevated levels of prostaglandins, 5HT and bradykinin have been reported, which lead to localized inflammatory response and progressive functional changes in dorsal horn and CNS (Tjolsen *et al*., 1992).In present study, formalin test was used because it describes the two phasic pains having different mechanism of nociception. Test drugs showed better effects than positive control i.e. paracetamol. In our study paracetamol did not show inhibition of first phase (0-5) minutes after formalin injection. However, in previous studies, the researchers have revealed that PCM inhibited both phases of formalin test (hunskaar and Hole, 1987; Choi *et al*., 2001; Luccarini *et al*., 2004). Fluvoxamine, (SSRI) also induced analgesia in animal models of acute pain. The oral effectiveness of fluvoxamine has not been scientifically studied in the past. Hence this study was designed to probe this phenomenon. The data obtained revealed that fluvoxamine was effective in different pain scoring behaviors of mice.

It showed maximum effect in chemically induced pain (acetic acid induced writhing and licking) and less effective in hot plate method. However, in formalin induced paw- lickingpaw-lifting, fluvoxamine showed approx. 100% pain protection in second phase. In hot plate test fluvoxamine was effective like citalopram than also had greater effect than all other test drugs. Serotonin and norepinephrine are the neurotransmitters that are involved in nociceptive circuit (Kranzler *et al*., 2001). Fluvoxamine via action on 5-HT pathway may significantly reduce number of writhes and licking (Fields *et al*., 1991). Results of the present study are in good agreement with earlier findings (Rojas-Corrales *et al*., 2003), confirming that antidepressants exhibit anti-nociceptive activity. Anti-nociception may be attributed to the involvement of drug interaction with other neurotransmitter system which acts on opioid receptors (Lowther *et al*., 1995). Another possibility may occur from indirect association with dopaminergic system (Schreiber and Pick, 1997). Citalopram at therapeutic concentration showed anti-nociceptive effects in acute pain models. The present results showed anti-nociceptive effects at different oral doses of citalopram (from low to high) on acetic acid induced pain, formalin induced persistent pain and hot plate induced thermal stimuli (Schreiber and Pick, 1997).

Anti-nociceptive effect of citalopram was found dose dependent. Our results are in little disagreement with earlier observation which showed that when citalopram was injected intraperitoneally, it produced weak anti-nociceptive effect showing negative dose response relationship. When assessed in acute model of nociception (hot plate test) in mice, citalopram was found ineffective (Bomholt *et al*., 2005). Present study showed that in hot plate assay (acute pain model) at therapeutic range 20mg/kg showed effectiveness. Reason may be due to essential role for 5-HT receptor in pain modulation (Suzuki *et al*., 2005). We administered citalopram orally while schreiber *et al* used intra-peritoneal route (Schreiber and Pick, 1997). The differences in route of administration of drug may lead to varied effects of drug metabolism in the intestine. Citalopram showed effectiveness in acetic acid induced writhing, licking and formalin induced licking and paw lifting. SRI (serotonin reuptake inhibitors) and NRI (norepinephrine reuptake inhibitors) significantly blocked

abdominal constriction in model of acute visceral pain and NRI have greater affinity as compared to SRI (Leventhal *et al*., 2007). SSRIs did not produce significant improvement in various pain models while SNRI have shown to be effective due to inhibition of monoamine transporter binding and have potent hydrogen binding affinity (Ardid *et al*., 1992). Present study showed positive results that may be due to reactive or non- reactive metabolites but needs more investigation to determine its exact mechanism. In the present study, duloxetine at 20mg/kg showed little effectiveness in hot plate induced thermal stimuli as compared with previous study that duloxetine at (3-30mg/kg i.p) significantly increased latency time to respond (Bomholt *et al*., 2005). Duloxetine showed effectiveness against first and second phase of licking and paw lifting that agreed with previous study in which citalopram and duloxetine at 30mg/kg i.p. significantly attenuated formalin induced nociception (Bomholt *et al*., 2005). Duloxetine reversed acetic-acid induced writhing in rats and also showed efficacy in reversing carrageenan and capsaicin induced hyperalgesia and allodynia at doses that showed limited effects on hot plate and tail flick test (Jones *et al*., 2005). Serotonin and norepinephrine reuptake inhibitors decrease pain inducing effects in part by activating G-protein signaling cascade (Raymond *et al*., 2001).

Increased levels of serotonin and norepinephrine in blood cause activation of different signaling pathways that have capacity to induce transcription of genes downstream by encoding hypothalamic hormone, serotonin receptors, components of non-serotonergic-system, neurotropic factors and inflammatory mediators (Kroeze *et al*., 2012). The present study demonstrates that oral dose of anti-epileptic drug lamotrigine produces anti-nociceptive effects. Comparatively weak effects were shown as compared to antidepressants and appeared to be test dependent. The mechanism of action of lamotrigine has been reported as blockage of voltage gated sodium channel and reducing neuronal depolarization (Kuo *et al*., 1997). It has been found to inhibit excitatory postsynaptic currents (EPSC) by blocking voltage gated sodium channel or calcium channel (Leach *et al*., 1986). Recent study suggested that structurally diverse compounds bind to amino acid residue in an overlapping but non-identical binding sites located in inner site of pore channel with different affinity and may account for their different therapeutic profile (Kuo *et al*., 1997). Our final aim of study was to determine comparative effects of antidepressants and anticonvulsant on different pain models of nociception.

We preferred to test our drugs on visceral pain model because it has diverse locality that's why it cannot be inhibited by traditional NSAIDs, secondly most prominent side effects of traditional pain killers make it difficult to use in patient with gastric ulcer. We selected safe clinically proved antidepressant and anticonvulsant drugs which are easily available in market. Citalopram, amitriptyline, fluvoxamine and duloxetine have limited adverse effects if these are used for short period of time. Secondly, some pain types need combination of pain killers and extra intervention to manage so there are chances of drug-drug interactions. Persistent pain model showed two phases of animal behavior. Hence we assessed different pain killers i.e. codeine, ibuprofen and tramadol (data not shown) as standard drugs but they showed poor effectiveness in phase 1 of formalin test. Antidepressants showed better results to inhibit phase 1 and also in phase 2 induced pain responses. In the same way pain due to central stimuli are difficult to manage. Majority of drugs remain ineffective in hot plate induced central sensitization but CTP, DXT, AMT, FLX and LTG showed significant effectiveness in acute pain models in mice.

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