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Comparative Effect of Antidepressants (Desipramine) and NSAID (Dexibuprofen) Against Chronic Pain and Depression Associated with MIA Induced Osteoarthritis in Rats.

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ABSTRACT

To compare the role of anti-depressants (Desipramine) and NSAID (Dexibuprofen) in monosodium iodo acetate (MIA) induced chronic knee osteoarthritis (OA) in rats. Twenty four male wistar rats were divided into 4 groups of 6 animals each. Group I to IV served as Vehicle control, OA control, Desipramine and Dexibuprofen treated groups respectively. Group I received I.A. Injection of 50µl of 0.9%normal saline, and Group II to IV received I.A. Injection of 50µl MIA, and the treatment of drugs started on the same day. The animals will be monitored for osteoarthritis parameters and/or depression on pre-dose day (day 0) and on day 1, 3, 5, 7, 11 14, 18, 21 and 28 th day. The rise in knee inflammation is almost similar in all MIA treated groups ($p<0.001$) on day 3. The inflammation reached to normal on day 7 and has slightly increased in desipramine group on day 7 to day 14, whereas the fluctuation is not seen in dexibuprofen group. Dexibuprofen increased Vocalization threshold of knee compression force for 7 days and decreased the rafter whereas desipramine has no effect for first 7 days and increased the rafter. Desipramine was significantly ($p<0.001$) effective on neuropathic pain (Punctate allodynia, mechanical grip strength, threshold angle of knee extension) and depression (forced swim test and locomotor activity) compared to dexibuprofen. The present study has shown that dexibuprofen has the potential in the initial phase of chronic OA and desipramine in the later stage, where neuropathic and depressive component dominates.

Keywords: Osteoarthritis, Depression, MIA, Desipramine and Dexibuprofen

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INTRODUCTION

Osteoarthritis (OA) is the leading joint disorder affects millions of individual's worldwide[1]. Significant studies revealed that there is a relationship between the chronic pain[2,3]and depression. There are no convincing evidences of therapeutic management concentrating on both chronic pain and its associated mania. Thus it is a global alarm for more studies to be conducted on the treatment regimen of OA associated pain and depression.

The currently available common treatments for OA include nonsteroidal anti inflammatory drug (NSAID) . Dexibuprofen, a NSAID is a well established drug in treating pain & inflammation [4,5]. The impact of analgesics in reducing pain induced depression is not studied. Desipramine is the tricyclic antidepressant (TCA) exerts antinociception effect [6-8] . There does not seem to be any study that has analysed the effect of antidepressants in reducing pain and depression in a single model.

The present study was undertaken to determine the pharmacological effect of Dexibuprofen and Desipramine in the rat model of Monosodium iodoacetate (MIA) induced OA to address both chronic pain and its associated depression in a single animal model.

MATERIALS AND METHODS

Experimental animals and induction of arthritis

Animals:

Healthy male wistar rats weighing about 150 – 200 g were obtained from institute animal Center. The protocol was approved by the institute's animal ethical committee (IAEC no. 126/bc/09/CPCSEA).

Experimental design:

Twenty four male wistar rats , were used in this study. The animals were randomized into 4 groups of 6 animals as per body weight.

Group 1: Vehicle control (50µl of 0.9% normal saline, I.A. injection)

Group 2: Osteoarthritis control (50µl of MIA, I.A. injection)

Group 3: MIA (50µl) + Desipramine (1 mg/kg, o.d)

Group 4: MIA (50µl) + Dexibuprofen (30 mg/kg, t.i.d)

The oral drug treatment is started on day 1 and continued upto day 28.

Induction of osteoarthritis:

After appropriate anaesthesia (ketamine 50mg/kg,i.p) each rat was positioned on its back and the right leg was flexed 90 degrees at the knee. Test group animals are treated with MIA (4 mg, 50

µl of 80mg/ml MIA dissolved in 0.9% sterile normal saline) by a single intra-articular injection through the intrapatella ligament of the right knee by using unit syringe fitted with 26G, 0.5 inch needle. Control group animals are treated with single intra-articular injection of MIA dose equivalent 0.9% sterile normal saline into the right knee. Treatment will be given to the MIA treated animals from 1st day to 28th day following OA induction[9-11]. The animals will be monitored for osteoarthritis parameters and/or depression on pre-dose day (day 0) and on day 1, 3, 5, 7, 11 14, 18, 21 and 28 th day.

OSTEOARTHRITIS ACTIVITY:

Measurement of Knee joint diameter:

The femorotibial joint diameter of right hind leg for both control (0.9% saline) and MIA (50µl) injected group animals were measured by using calibrated digital caliper. The unit of joint diameter was expressed as (mm)[12-13].

Evaluation of Mechanical Hyperalgesia:

The vocalisation threshold of knee compression was measured with the help of forceps fitted with pressure gauge having the length of 20 cm long and 4mm X 4mm contact area. The pressure was applied continuously over the knee joint until an audible squeak was elicited. The output voltage was calibrated as grams of force [13].

Measurement of Punctate allodynia:

Punctate allodynia was assessed based on the withdrawal thresholds to calibrated von Frey hairs. A maximal cut off of 15 g was used .Animals were placed in Plexiglas boxes with a mesh flooring giving access to the underside of their paws and allowed to acclimatize for at least 30 min. Allodynia was evaluated by application of von Frey hairs in ascending order of force for up to 6 s to the plantar surface of hind paws. The lowest amount of force required to elicit a response was recorded as paw withdrawal threshold (PWT) in g [12, 14-16].

Assessment of Grip strength:

Rota rod instrument was used to assess grip strength and muscle co-ordination . The duration of animal grasping the revolving rod (10 cm diameter; 16 rounds per min, 20 rpm) was recorded either by manually or automatically depending upon the instrument. The cut off time for this test is 180 sec. During the time of riding, if the animal doesn't fall within 180 sec the animal was released from the revolving rod[14-17].

Weight bearing:

An incapacitance tester (Linton Instrumentation, Norfolk, UK) was employed for determination of hind paw weight distribution. Rats were placed in an angled plexiglass chamber positioned

so that each hind paw rested on a separate force plate The force exerted by each hind limb (measured in grams) is averaged over a 5-s period. Each data point is the mean of three, 5-s readings. The change in hind paw weight distribution was calculated by determining the difference in the amount of weight (g) between the left and right limbs. Results are presented as the difference in weight bearing between the left (contralateral control) limb and right (osteoarthritic) limb[11].

Struggle threshold angle of knee extension:

The study was done as described by Yu YC et al, 2002. The rat was gently restrained by one hand to measure the struggle threshold of knee extension. While holding the rat in the palm, the leg was extended to determine the knee extension angle at which the rat showed struggling behaviour. The extension angle was then calculated by trigonometric function using the length of the tibia and the foot travel distance during extension[13].

DEPRESSENT ACTIVITY

Depressant and psychological activity is assessed by Forced swim test and Actophotometer.

Forced swim test:

The Forced swim test (FST) was carried out according to Porsolt etal. During the test session the following behavioural responses were recorded: climbing behavior, which is defined as upward-directed movements of the forepaws along the side of the swim chamber; swimming behavior, defined as movement throughout the swim chamber, which include crossing into another quadrant; and immobility time, that was considered. The rat was judged immobile if it floated in the water in an upright position and makes only little movements to keep its head above the water or made other passive movements[14-16].

Spontaneous Locomotor Activity:

To evaluate spontaneous locomotor activity, each animal was individually placed in an actophotometer. The photocells of the actophotometer were checked before use and the animals were individually placed in a square arena (30 x 30cm). After an initial accustomed period (2 min), the locomotor scores were recorded digitally for the next 10 min[15-16].

Measurement of Body Weight

Body weights of each group animals were measured at alternative days by using weighing balance, still to the drug treatment and the changes were recorded.

Statistical Analysis:

The data are expressed as the mean± standard error of mean (SEM). Statistical analyses were conducted by two way analysis of variance (ANOVA), followed by Bonferroni post test to

compare means among groups at every time points. A *P*-value of less than 0.05 was considered to be significant.

RESULTS AND DISCUSSION

The inflammation has reached near to normal on 7 th day in both treatment groups (Figure 1) compared to positive control with more reduction in Group-IV. The inflammation has slightly increased in desipramine group on day 7 to day 14, whereas the fluctuation is not seen in dexibuprofen group. Dexibuprofen had shown significant ($p<0.001$;Figure 2) inhibition in mechanical hyperalgesia compared to MIA induced animals before day 3, and desipramine after day 7. The paw withdrawal threshold, mechanical grip strength, hind paw weight distribution, and threshold angle of knee extension as shown in Figure 3-6 respectively increased in treatment groups and it is more prominent in Group III ($p<0.001$). Figure-7 & 8 shows the results of forced swim test and locomotor activity. Group-III has shown good antidepressant activity compared to other treated groups. Drug treated animals (Group-III to IV; Figure 9) improved the body weights, where the increase is significantly ($p<0.001$) higher in Group-IV.

Osteoarthritis (OA) related pain has been attributed to local tissue injury causing nociceptive, neuropathic pain and depression[18 -19]. After 3 days post injection of MIA (Group II; Figure 1), brief period of inflammation was noted which reduced to normal levels by day seven as previously reported by Fernihough J et.al, 2004 [12] Dexibuprofen decreased the knee inflammation [Figure 1] significantly ($p<0.001$) from day 3 to day 7, and does not increase further till day 28, whereas, the inflammation has gradually increased after day 7 in dexipramine group. This shows that dexibuprofen has major role in reducing OA induced inflammation than desipramine.

Compared to desipramine, dexibuprofen significantly ($p<0.001$)reduced hyperalgesia at day3 [Figure 2] following MIA injection, when there is measurable knee joint swelling, After day 7, dexibuprofen has no effect on increasing compression threshold, whereas desipramine increased the threshold after day 7. This suggest an early component of inflammatory nociceptive pain as reported earlier for NSAIDs[12] and neuropathic pain in later periods. Neuropathic pain seems to be mostly due to non-inflammatory mechanisms due to the stimulation of low-threshold (Aβ) inputs [20] . Actually, joint compression likely augments stimulation of high-threshold (Aδ/C) afferent fibers and prolonged injury activates low-threshold (Aβ) input and results in either peripheral or central sensitization [20]. Animal model studies have demonstrated potent facilitation of the joint (Aβ) afferents following induced joint inflammation[21], induced monoarthritis

(carrageenan/kaolin)[22], and intra-dermal capsaicin-induced central sensitization [23] and MIA induced OA. Also, sensitization of these peripheral nerves leads to enhanced mechano sensation in the affected joint, reflected as allodynia, hyperalgesia, and shift in weight bearing [23].

Punctate allodynia was detected in all MIA-treated rats from day 7 until day 28 (Figure 3). It is signalled by Aδ primary sensory neurones. In humans, the origin of OA associated joint pain is thought to be due to the stimulation of C-fibres and Aδ nerve endings in the Synovium and surrounding joint structures, such as ligaments and muscles [9]. Desipramine significantly ($p<0.001$) increased the threshold from day 7 demonstrating the effect on OA associated joint pain through Aδ primary sensory neurons.

Desipramine showed significantly ($p<0.001$) enhanced Grip strength (Figure 4), and weight bearing (Figure 5) compared to dexibuprofen, whereas a similar response was seen in knee extension threshold (Figure 6) . The lack of effect for dexibuprofen in grip strength and weight bearing at later time points suggest a potential neuropathic pain component of MIA-induced pain at these time-points.

A significant ($p<0.001$) antidepressant activity has been noticed for desipramine in forced swim test (Figure 7) and locomotor activity (Figure 8), but not with dexibuprofen. The significantly ($p<0.001$; Figure 9) increased weight gain noticed with the desipramine, could be due to its effect on normalizing the serotonin level and analgesic effect as reported earlier[24-26].

The current study reveals that the antidepressants have the potential to be a useful adjuvant in the treatment of chronic OA. More studies has to be done to analyse other potential antidepressants alone and in combination with NSAIDs to address the complexity of symptoms associated with chronic OA.

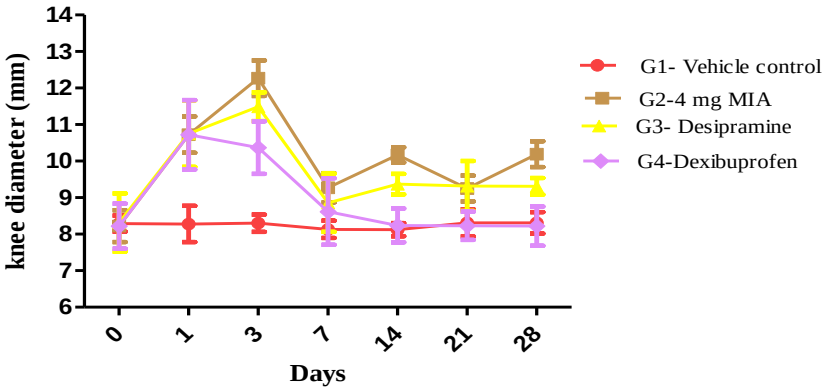

Figure 1: Comparative effect of Desipramine and Dexibuprofen on knee joint swelling in MIA induced OA and depression in rats. Values are in Mean ± SEM.

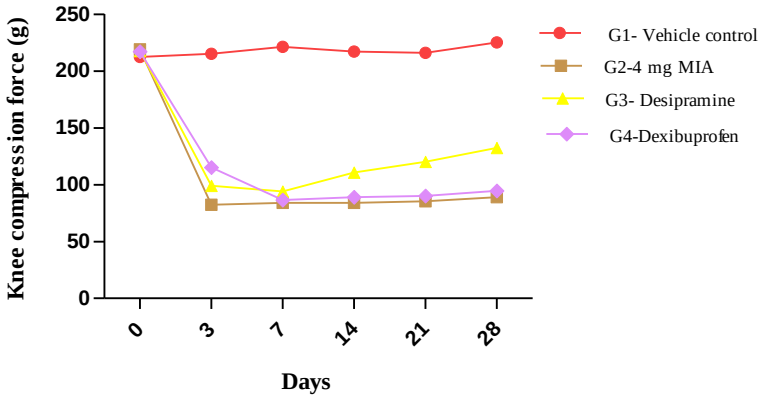

Figure 2: Comparative effect of Desipramine and Dexibuprofen on muscle coordination in MIA induced OA and depression in rats. Values are in Mean ± SEM.

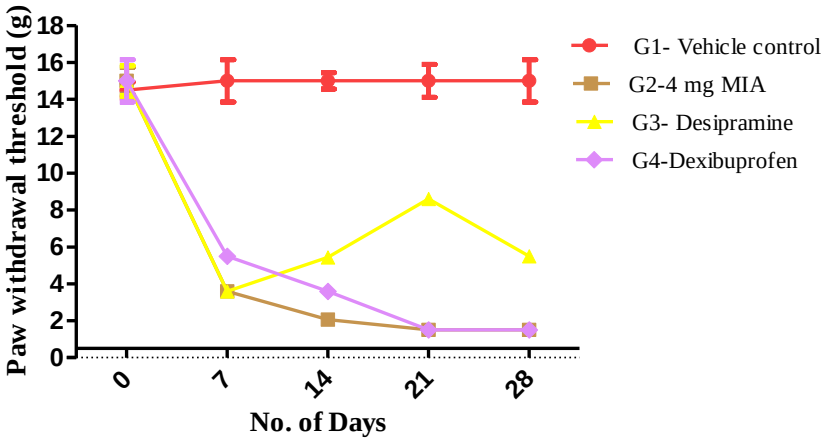

Figure 3: Comparative effect of Desipramine and Dexibuprofen on paw withdrawal threshold to von Frey filament stimulation in MIA induced OA and depression in rats. Values are in Mean ± SEM.

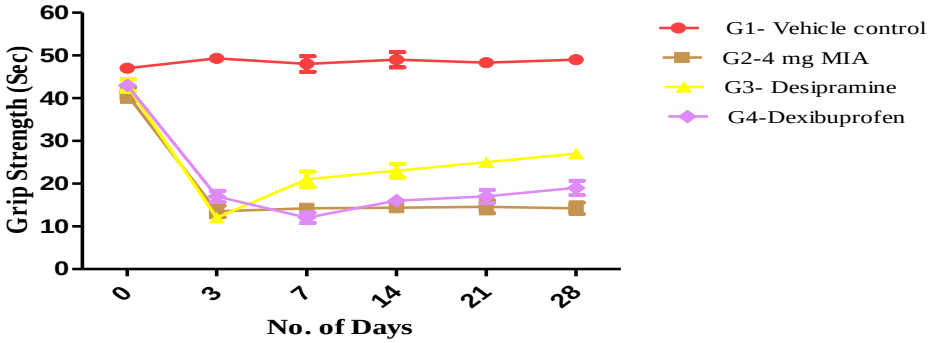

Figure 4: Comparative effect of Desipramine and Dexibuprofen on muscle coordination in MIA induced OA and depression in rats. Values are in Mean ± SEM.

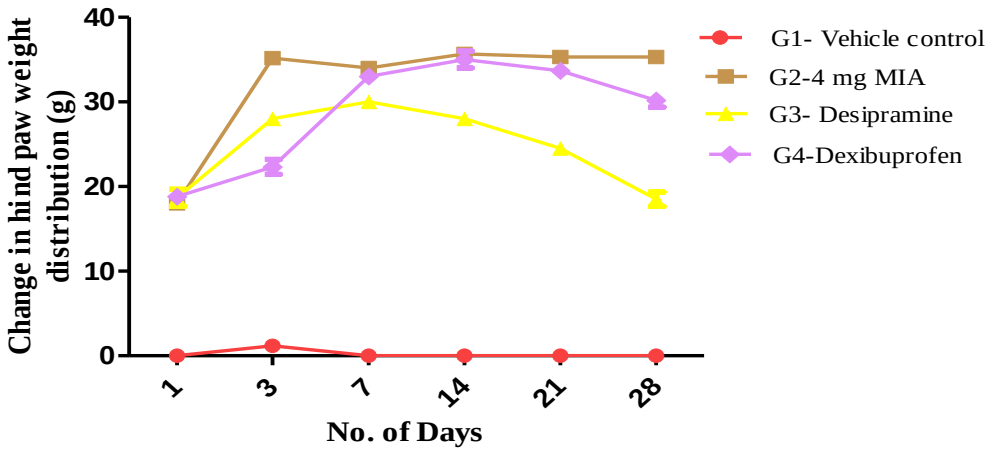

Figure 5: Comparative effect of Desipramine and Dexibuprofen on weight bearing in MIA induced OA and depression in rats. Values are in Mean ± SEM.

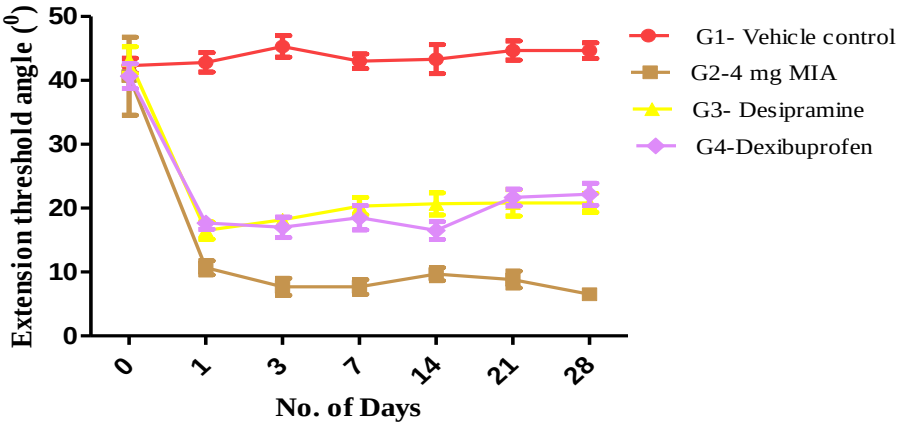

Figure 6: Comparative effect of Desipramine and Dexibuprofen on threshold angle of the knee extension in MIA induced OA and depression in rats. Values are in Mean ± SEM.

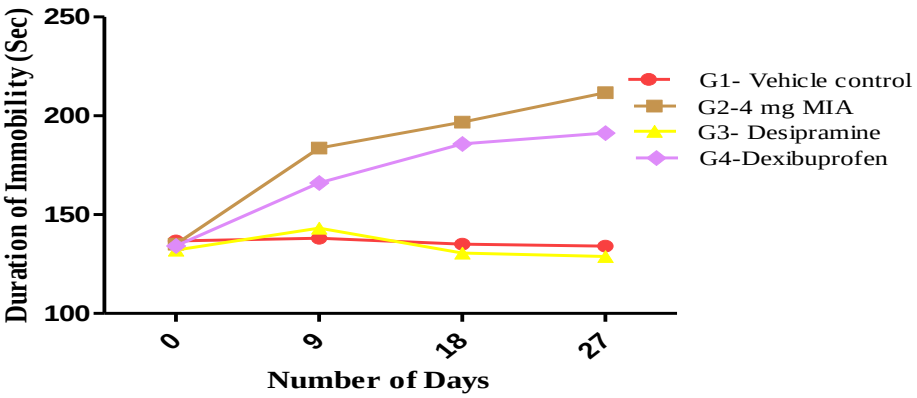

Figure 7: Comparative effect of Desipramine and Dexibuprofen on locomotor activity in MIA induced OA and depression in rats. Values are in Mean ± SEM.

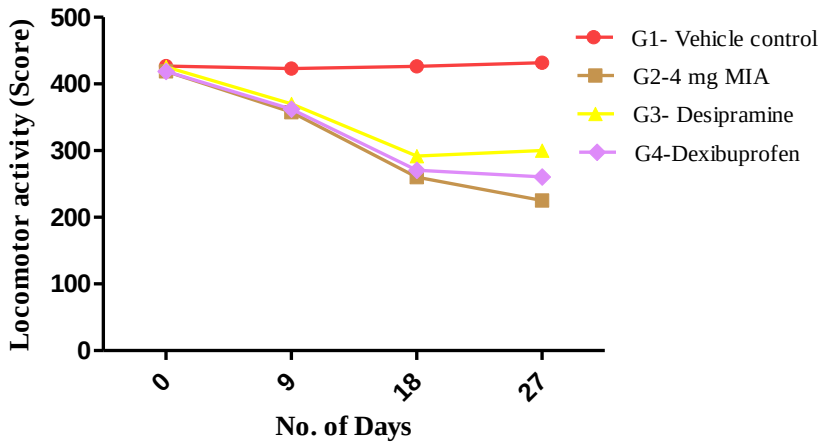

Figure 8: Comparative effect of Desipramine and Dexibuprofen on forced swim test in MIA induced OA and depression in rats. Values are in Mean ± SEM.

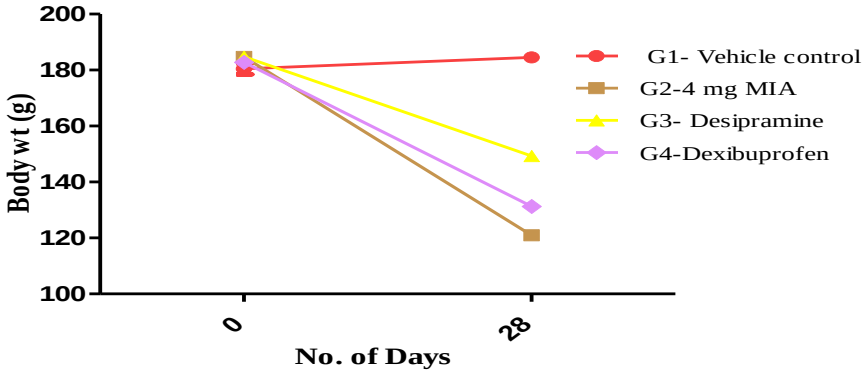

Figure 9: Comparative effect of Desipramine and Dexibuprofen on animal body weight in MIA induced OA and depression in rats. Values are in Mean ± SEM.

CONCLUSION

Chronic OA is a complex disease associated with neuropathic, nociceptive and depressive mechanisms. Currently approved therapies address either of these and not completely. The present study has shown that the NSAIDs has the potential in the initial phase of chronic OA and desipramine in the later stage, where neuropathic and depressive component dominates.

REFERENCES-

1. Martel-Pelletier J, Wildi LM, Pelletier JP, Future therapeutics for osteoarthritis. Bone 2012 ;(2):297-311.
2. Bair, MJ, Robinson RL, Katon W, Depression and pain co-morbidity: a literature review, Arch. Intern. Med 2003;163:2433–2445.
3. Wilcox S, Brenes GA, Levine D, et al. Factors related to sleep disturbance in older

adults experiencing knee pain or knee pain with radiographic evidence of knee osteoarthritis. J Am Geriatric Soc 2000; 48:1241–51.

4. Hawel RG, Singer F, et al. Composition of the efficacy and tolerability of Dexibuprofen and Celecoxib in the treatment of osteoarthritis of the hip. In J Clin Pharmacol Ther 2003;41: 153-164.
5. Singer F, Mayrhofer F, Klein G, Hawel R, Kollenz C J. Evaluation of the efficacy and dose-response relationship of Dexibuprofen in patients with osteoarthritis of the hip and comparison with Ibuprofen using the WOMAC osteoarthritis index. Int J Clin Pharmacol Ther 2000;38: 15-24.
6. Carlsson A, Corrodi H, Fuxe K, et al. Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-a-ethyl-meta-tyramine. Eur. J. Pharmacol 1969;5:357-366.
7. Ward NG, Tricyclic antidepressants for chronic low back pain: mechanism of action and predictors of response, Spine 11, 986, 661-665.
8. Max MB, Kishore-Kumar R, Schafer, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain 45: 3-9.
9. Combe R, Bramwell S, Field MJ, The monosodium iodoacetate model of osteoarthritis: a model of chronic nociceptive pain in rats. Neurosci Lett 2004;370(2-3): 236-40 .
10. Kalbhen DA, Chemical model of osteoarthritis-a pharmacological evaluation, J Rheumatol 1987;14:130-1.
11. Bove SE, Calcaterra SI, Brooker ML, Huber CM, Guzman RM, Juneau PL, Weight bearing as a measure of disease progression and efficacy of anti-inflammatory compounds in a model of monosodium iodoacetate-induced osteoarthritis, Osteoarthritis and Cartilage 2003;11: 821–830.
12. Fernihough J, Gentry C, Malcangio M, Fox A, et al. Pain related behavior in two models of osteoarthritis in the rat knee. International association for the study of pain 2004;112: 83-93.
13. Yu Y, Koo S, Kim CH, Lyu Y, Grady JJ, Chung JM, Two variables that can be used as pain indices in experimental animal models of arthritis. J Neuroscience Method 2002;115:107-103.
14. Karel-Martijn K , Mohammed El M , Jan van E et al. Pre-treatment with capsaicin in

a rat osteoarthritis model reduces the symptoms of pain and bone damage induced by monosodium iodoacetate. Eur J Pharmacol 2010;1:108-13

15. Choi JI, Kim WM, Yoon MH, Lee HG. Antiallodynic Effect of Thalidomide and Morphine on Rat Spinal Nerve Ligation-induced Neuropathic Pain. Korean J Pain, 2010;23(3):172–178.
16. Dias JP, Ismael MA, Pilon M et al. The kinin B1 receptor antagonist SSR240612 reverses tactile and cold allodynia in an experimental rat model of insulin resistance.,Br J Pharmacol 2007;152(2):280–287.
17. Niklas S, Jason J, Grading of monosodium iodoacetate-induced osteoarthritis reveals a concentration-dependent sensitization of nociceptors in the knee joint of the rat, Neuroscience Letters 2009;465:184–188.
18. Hochman JR, Gagliese L, Davis AM, Hawker GA, Neuropathic pain symptoms in a community knee OA cohort, Osteoarthritis and Cartilage 2011;19(6):647-65.
19. Lin EH, Depression and Osteoarthritis, T Am J Med. 121 (11) , 2008 , S16-9.
20. Courtney CA, Witte PO, Chmell SJ, Hornby TG, Heightened flexor withdrawal response in individuals with knee osteoarthritis is modulated by joint compression and joint mobilization, J Pain 2010;11(2):179-85.
21. Ferrell WR, Wood L, Baxendale RH, The effect of acute joint inflammation on flexion reflex excitability in the decerebrate, low-spinal cat, Q J Exp Physiol 1988;73: 95-102.
22. Weng HR, Laird JM, Cervero F, Schouenborg J, GABA A receptor blockade inhibits A beta fibre evoked wind-up in the arthritic rat. Neuroreport 1998;9:1065-1069.
23. Rudomin P, Hernandez E, Changes in synaptic effectiveness of myelinated joint afferents during capsaicin-induced inflammation of the footpad in the anesthetized cat, Exp Brain Res 2008;187:71-84.
24. Neupert W, Brugger R, Euchenhofer C, Brune K, Geisslinger G, Effects of Ibuprofen enantiomers and its coenzyme A thioester on human prostaglandin endoperoxide synthases. British J Pharmacol 1997;122:487-92.
25. Wurtmann JJ. Depression and weight gain: the serotonin connection. J Affective Disorders 1993;29:183-192.
26. Lake JK, Power C, Cole TJ. Back pain and obesity in the 1958 British birth cohort. cause or effect. J Clin Epidemiol 2000;53(3): 245-50.