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EFFECTIVE TREATMENT OF HIV INDUCED NEUROPATHY

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Abstract:

Human immunodeficiency virus (HIV) is RNA retrovirus which causes damage of immune defense cells ultimately self-defense system of human body weakens. Its characteristic phase known as acquired immune deficiency syndrome (AIDS). A staggering amount of 33 million people are living with HIV worldwide. Approx. 2 million people died almost every year and 2.5 million new cases are reported every year. 70% of this population lives in Africa, 20% is in Asia and 10% is in the rest of the countries. HIV virus and antiretroviral drug (Zidovudine, Didanosine etc.) can causeperipheral injury which affects sensory nerve, motor nerves, thoracic nerve, cranial nerve as well as autonomic nerve and called HIV neuropathy (HIV-NP). HIV-NP is worldwide syndrome nevertheless maximum ratio of patients present in South Africa. Peripheral neuropathy (PNP) is one of the major complications in HIV patients which may HIV majorly affects multiple sensory and motor nerves in the distal part of the limbs, called polyneuropathy. In this mostly people experience unusual sensation, numbness, and pain in their hands and feet and even touching can cause pain sensation. HIV sometimes can affect one nerve at a time which leads to pain, called Mononeuropathy. DSP (distal symmetric polyneuropathy) was recognized as a common neurological manifestation of AIDS, it is characterized by distal degeneration of long axons. Numerous treatment strategies were followed for HIV-NP like lamotrigine, capsaicin, cannabis etc. Here I reviewed many models for HIV neuropathy, for example, Model of HIV encephalitis (HIVE), humanized mouse model etc.

KEYWORDS: *Peripheral Neuropathy, Distal Symmetric Polyneuropathy, Polyneuropathy, Mononeuropathy, HIV.*

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Introduction

HIV/AIDS:

HIV virus weakens immune defense cells that lead the loss of $CD4^+$ T cells andit shows one of the characteristic features that name calledacquired immune deficiency syndrome (AIDS). It shows the harmful effect in an average of 8 to 10 years with casualties, or diseases that only cause illness in people with weak function of immune system [1]. HIV is aconstant (lifelong)infection and can be treated by some medications. In the biological world, generally genetic data is stored in DNA and then DNA is rewritten into RNA and then RNA translated into proteins (structural and functional proteins). The genetic information of the HIV virus stay is in RNA, so when it enters inside the body cell it carries its genetic information in the form of RNA. HIV virus keeps on carrying the reverse transcriptase enzyme [2]. A staggering amount of 33 million people are living with HIV worldwide. Approx. 2 million people died almost every year and 2.5 million new cases are reported every year. 70% of this population lives in Africa, 20% is in Asia and 10% is in the rest of the countries [3].

Here in this article discussed variouskind of HIV patients turns in more severe conditions or disease called neuropathic pain examples are likeperipheral neuropathies, HIV-associated sensory neuropathies, Distal symmetric polyneuropathy,Mononeuritis, multiplex, Acute inflammatory demyelinating polyneuropathy, Antiretroviral toxic neuropathy, Autonomic neuropathy, Neuropathy in diffuse infiltrative lymphomatosis syndrome, Chronic inflammatory demyelinating polyneuropathy and Neuropathies due to opportunistic infections [4]. HIV-NP is found that named as distal sensory polyneuropathy (DSP) which mainly associated with causative agent of HIV and treatment of HIV via antiretroviral treatments. The frequency and prevalence of DSP, however, remain high and may be increasing. Majorly antiretroviral drugs include for the treatment of HIV called HAART therapy. Various clinical reports are mentioned in AIDS Clinical Trial Group (ACTG) Study 384 [5], the number of patients who have HIV neuropathy is increasing worldwide.

HIV to Neuropathy

Neuropathy is one of the common complications in HIV patients; it is a type of disorder of peripheral nerve with increasing survival of patients with HIV-NP resultant increasing worldwide.The mechanism of HIV-NP is accidental causes by proteins gp120 (envelope

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protein) which may damage or injury in axonalthrough the Schwann cells and affects peripheral sensory, motor nerves, thoracic nerve, cranial nerve, autonomic nerve [4].Neuropathy caused due to a group of antiretroviral drugs called antiretroviral toxic neuropathy which may affect single nerve at a particular time and cause pain called mono-neuropathy.HIV affects two or more than two (united) sensory and motor nerves in a distant part of the limbs; this type of neuropathy is called polyneuropathy. The patient suffers from unusual sensation, numbness, and pain in their hands and feet confirmed by touching (can cause pain sensation)[4].

Distal symmetric polyneuropathy (DSP):- DSP (distal symmetric polyneuropathy) was recognized as a common neurological manifestation of AIDS. It is characterized by distal degeneration of long axons which degenerate first fibers from distal regions with centripetal progression resultant decrease the density myelinated and unmyelinated fibers. Common risk factors for pheripheral HIV neuropathy are like Advanced disease, CD4 count<100 cells/mm^3, History of neuropathies, Use of neurotoxic drug, Nutritional deficiencies, Aging with decreased neurologic function.Drugs used for HIV treatment may also cause neuropathy pain for example zalcitabine, didanosine, stavudine these medications inhibit neurite outgrowth and mitochondrial DNA synthesis and finally it cause neuropathy pain [6]. It occursin 8% to 21% of stavudine users and 17% to 20% of didanosine users[7].

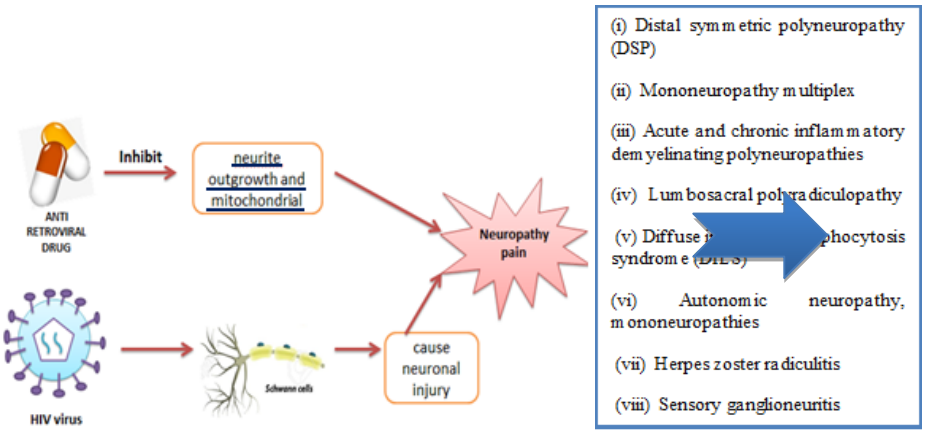

Fig.1 HIV virus and anti-retroviral drug cause different types of neuropathic pain

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Prevalence of HIV neuropathy (HIV-NP): Limited number of articles gives a correct prevalence of HIV-NP and mentioned in table 1.

Table 1. Prevalence of HIV-NP

Country	Patient suffering from HIV neuropathy	Reference
South Africa	57%	[8]
Australia	42%	[9][2]
Sub-Saharan Africa	22%	[10]
Zambia	11.9%	[11]
Uganda	53%	[12]

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Neuropathy induced after the treatment of anti- retroviral drug: Due to the longer duration of time and higher concentration of drugs may damage the somatosensory system due to gp120 protein through shwan cells. In below table Class of drugs, their mechanism, and side effects are properlymentioned.

Table 2: Reported activity of anti-retroviral drug

Sr.No	Class	Drug	Mechanism of action	Side effect	Reference
1.	Nucleoside reverse transcriptase inhibitor (NRTIs)	Zidovudine	It will undergo phosphorylation, then zidovudine triphosphate selectively inhibit viral reverse transcriptase, so at the end single stranded viral RNA will not convert to double stranded proviral DNA.	Anemia, neutropenia, anorexia, abdominal pain, insomnia and myalgia.	[13]
2.		Didanosine	It will intracellularly convert to didanosine triphosphate, then it will compete with ATP for incorporation into viral DNA, inhibit HIV reverse transcriptase and terminate proviral DNA.	**Neuropathy**, acute pancreatitis, diarrhea, abdominal pain.	**[14]**
3.		Stavudine	It will convert to thymidine with the help of thymidine kinase. It selectively inhibit viral reverse transcriptase and it will not allow single stranded RNA to convert into double stranded DNA.	On combination with didanosine it causes peripheral neuropathy. Lipodystropy, lactic acidosis and pancreatitis.	[15]
4.		Lamivudine	It is deoxycytidine analogue. It phosphorylated intracellularly and inhibits HIV reverse transcriptase as well as HBV DNA polymerase. It will incorporate into DNA and cause chain termination.	Headache, fatigue, rashes nausea, anorexia, abdominal pain.	[15]
5.		Abacavir	It is guanosine analogue; it will intracellularly convert to carbovir triphosphate, which get incorporated in proviral DNA and terminates chain elongation. Rapid reduction in HIV RNA count and rapid rise in CD4 cell count has been noted.	Hypersensitivity reaction, lypodystrophy.	[16]

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6		Tenofovir	It is only nucleotide analogue. Tenofovir release from hydrolysis of the prodrug is dephosphorylated by cellular kinases into tenofovirdiphosphate which preferentially inhibit HBV-DNA polymerase and HIV reverse transcriptase.	Nausea, flatulence, abdominal discomfort, loose motion. Renal toxicity is rare.	[3,17]
7.		Nevirapine	It is a non-competitive inhibitor, it directly inhibit reverse transcriptase enzyme without any use of intercellular phosphorylation. This drug block the polymerase point of reverse transcriptase and make it dysfunctional	Rashes, nausea, fever and rise in transaminases occurs.	[18]
8.		Efavirenz	Non competitively inhibit reverse transcriptase enzyme without any need of intracellular phosphorylation	Rashes, insomnia, neuropsychiatric symptoms, teratogenicity	[15]
9	Retroviral protease inhibitor	Atazanavir	Protease enzyme breaks polyprotein chain into small functional proteins. Atazanavir bind to the active site of protease enzyme, interfere with its breakdown process, so at the end HIV infected cell produce immature noninfectious viral	Jaundice	[18]
10.		Indinavir	Action of this drug is same as atazanavir, it will also inhibit the break down process of protease enzyme, and at the formation of immature noninfectious viral progeny.	Nephrolithiasis, hyperbilirubinaemia.	[13]
11.		Nelfinavir	It will bind to the active site of protease molecule and interfere with the cleaving function of the protease enzyme.	Diarrhea and flatulence.	[19]
12.		Ritonavir	It will also interfere with the cleaving function of protease enzyme by attaching on the active site of the enzyme and at the end their will be no fictional protein form.	Paresthesias, fatigue,	[18]
14	Fusion inhibitor	Enfuvirtide	It binds to HIV1 envelop trans membrane glycoprotein (gp41) and did not allow fusion between HIV virus and host cell.	Injection is painful and cause local nodules/cysts.	[20]
15	CCR5 receptor inhibitor	Maraviroc	Maraviroc target CCR5 receptor and block it on the surface of the host cell, attachment of the virus and subsequent entry of viral genome into the cell is thus interfered.	Increase risk of malignancy	[21]

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16	Integrase inhibitor	Raltegravir	The HIV-proviral DNA transcripted in the cytoplasm of the host cell translocate to the nucleus along with an integrase enzyme. The HIV integrase nicks host chromosomal DNA and integrate the proviral DNA with it. Raltegravir is the orally active drug which will inhibit this enzyme.	Myopathy	[22]

DRUGS FOR HIV NEUROPATHY

Table 3: Reported activity of Anti- Neuropathy drug.

Sr.no	**Anti-neuropathy drug**	**Case study**	**Mechanism of action**	**Side effect**	**Result**	**Reference**
1.	Lamotrigine	1.Lamotrigine given to the number of patient receiving anti-retroviral therapy 2. Lamotrigine also given to number of patient not receiving antiretroviral therapy.	Sodium channel blocker	Dangerous skin reaction, myoclonic jerk, teratogenicity	Lamotrigine is effective in the patient receiving anti-retroviral therapy	[23]
2.	Nortriptyline with hydrocodone-acetaminophen	46 year old women suffering from HIV from last 17 years, over the year she develops worsening pain in her feet. She is also not tolerable to certain drugs. Gabapentin and duloxetine is given but due to their Side effect they are discontinued and finally nortiptaline whit hydrocodone-acetaminophen is given.	It will inhibit the reuptake of serotonin and non-epinephrine.	Constipation	Nortriptyline with hydrocodone-acetaminophen is better than other drug, even though it have side effect which is controlled by using senna and docusate. So Due to the difficulty in treating her, additional testing was pursued to confirm the diagnosis of small fiber neuropathy.	[24]

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3	Capsaicin	NGX4010 a low concentrated capsaicin patch is applied on the 307 patients suffering from HIV-DSP .NGX-4010 or control was applied once for 30, 60, or 90 minutes to painful areas on the feet.	Capsaicin desensitize cutaneous nociceptors which will cause reduction of pain	Mild-to-moderate local skin reactions	Mean pain reductions in the NGX-4010 30-, 60- and 90-minute groups were 27.7%, 15.9%, and 24.7% .One third of NGX-4010-treated patients reported ≥30% pain decrease as compared to 18% of controls	[25]
4	Recombinant human nerve growth factor (rhNGF)	270 patient having HIV neuropathy were given μg/kg rhNGF, or 0.3 μg/kg rhNGF by subcutaneous injection twice weekly for 18 weeks, then at the end observation is noted down.	It will stimulates the regeneration of damaged nerve fibers and reduce the pain	Pain in site of injection	Both dose of NGF will cause reduction of neuronal pain and it is also safe and well tolerated	[26]
5	Cannabis	Out of 55 patients of HIV neuropathy, 27 were randomized to cannabis cigarettes and 28 were randomized to placebo cigarettes. Thirty randomized patients completed the experimental pain model portion of the study (14 cannabis, 16 placebos). Observation is don till 5 days	It will inhibit the release of pain transporters.	Include anxiety and panic, teratogenicity	Group of patient who smoke cannabis 3 times a day reduce neuropathy pain 34% and 17% in case of placebo patients	[27]
6	Vicriviroc	There are 118 number of patients out of which 90 is treated with vicriviroc (5 mg, 10 mg, and 15 mg)and 28 on placebo.	Vicriviroc binds to the C-C chemokine receptor type 5 and prevents entry of HIV.	Common side effect	Vicriviroc therapy did not result in a statistically significant difference relative to placebo in PN	[6,28]
7	Nerve growth factor (NGF)	235 subjects is given with NGF 0.1 or 0.3 mg/kg subcutaneously twice weekly .these patients are divided into 4 group (A, B, C and D). Subjects were instructed to note their average and maximum neuropathy pain every day. Severity of neuropathy was assessed by neurological examination and quantitative sensory testing .comparison is done between all the four groups.	modulates the activity of small sensory nerve fibers, hence NGF is a potential target for intervention in DSP	Not known side effect	74 of the 95 subjects using dideoxynucleosideantiretroviral s in the double-blind phase continued their use and an additional eight subjects started taking these drugs in the open-label phase. 68 subjects did not complete the study. There were no significant differences in the duration of study participation among the four subject groups	[29]

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8.	Gabapentin (GBP)	15 patient is treated with gabapentin and 11 patient is treated with placebo, patients are under screening for I week, a 4 week double blind, and 2 week open treatment phase.(amount of drug:- 400mg/d 1st week, 1200 mg/d for 2 week and finally it may increase to 2400 mg/d)	It does not have any direct GABAergic activity, but it can effect α2-δ calcium channels, which help in pain reliving effect, GBP also inhibit ectopic discharge activity from injured nerves.	Somnolence, dizziness	In gabapentin group there was decrease in the pain up to 2.85 (-44.1 %) as well as of the sleep VAS to 2.3 (-48.9 %). No significant decrease in the pain in case of placebo group.	[30]
9	Amitriptyline or mexiletine	145 patients treated equally with amitriptyline, mexiletine, or matching placebo for randomized, double blind, 10 weeks trials. Final result is measured by measuring change in pain intensity between baseline and final visit	Amitriptyline inhibit the membrane pump mechanism which will block the reuptake of norepinephrine and serotonin in adrenergic and serotonergic neurons	Confusion, convulsions, dilated pupils and other eye problems	Improvement in amitriptyline group (0.31+/-0.31 units) In case of mexiletine (0.23+/-0.41) and in case of placebo (0.20+/-0.30). so both the drug (Amitriptyline and mexiletine) not able to provide significant pain relief in patients with HIV-associated painful sensory neuropathy.	[31]
10	Prosaptide (PRO)	Prosaptide is administered in the group of patient suffering from HIV neuropathy (2, 4, 8, or 16 mg/d). Other group is administered with PRO against placebo (PBO).(2, 4, 8, or 16 mg/d).this process is continued for 6 weeks and finally formed a post-hoc evaluation of an electronic diary (ED) to record HIV-associated neuropathic pain.	Activates the MAPK pathway by a G-protein-dependent	No adverse events or laboratory toxicities.	237 participants were randomized. The 6-week mean (sd) Gracely pain scale changes were -0.12 (0.23), -0.24 (0.35), -0.15 (0.32), -0.18 (0.34), and -0.18 (0.32) for the 2, 4, 8, 16 mg, and PBO arms respectively. Treatment with prosaptide was safe but it is not effective in the treatment of hiv neuropathy pain .	[32]

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11	Acetyl carnitine	A group of people having painfun neuropathy due to antiretroviral therapy were treated with acetyl-I-carnitine for 4 weeks, Each subject was evaluated by means of the modified Short Form McGill Pain Questionnaire (Melzack, 1987) with each item rated on an 11-point (0–10) scale at baseline and then at the end of each week, each subject is also evaluated by electromyography. Safety data were collected during this process	Direct analgesic role related to glutamatergic and cholinergic modulation	No adverse events	In this experiment statistically significant at week 3 (p ¼ 0.006) and at week 4 (p ¼ 0.003), while pain intensity did not significantly change at weeks 1 and 2	[33]
12	Memantine	45 subjects (24 induced with memantine and 24 with placebo) having HIV neuropathy enrolled in a randomized, multicenter, 16-week placebo-controlled study of memantine, an N-methyl-D-aspartate (NMDA) uncompetitive antagonist. First 6 weeks, 20 out of 24 reach to maximum maintained dose of 40 mg. At week 16, the percentage of subjects on memantine 40 mg, 30 mg, 20 mg, and 10 mg were 53%, 14%, 29%, and 5%, respectively. Out of this 3 of 21 subjects assigned to placebo and 4 of 24 were assigned with memantine discontinued treatment before completion of the study.	It will inhibit NMDA receptor non competitively	Tiredness, body aches	There were no significant different between the two group. Drug will not show decrease in the pain.	[34]
13	Pregabalin	Randomized, double blind and placebo-controlled- they included a 2 week double blind dose adjustment phase, after that maintenance phase for 12 week, then 3 months of optional open lab extension phase. At last two type of measurements taken, primary NPRS (Numeric Pain Rating Scale) and secondary PGIC (Patient Global Impression of Change)	Inhibit the alpha2-delta subunit of the voltage-gated calcium channels in central nervous system tissues located in the brain and spinal cord.	Somnolence and dizziness	NPRS score was 6.93 for phase randomization to pregabalin (n=151), 6.72 for placebo(n=181). Drug show greater improvement. This drug is well tolerated, but it is not showing good efficacy to placebo in the treatment of HIV neuropathy.	[26]

PATENT

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Table 4: Reported patent for HIV Neuropathy.

Sr. No.	Title/year	Patent no.	Inventors	Company
1	TOPICAL FORMULATIONS FOR TREATMENT OF NEUROPATHY/2011	US 20110178177A1	Richard Wolicki, Imperial Beach, CA(US); Stanley Kim, san Diego, CA(US)	TARAXOS INC., San Diego, CA (US)
2	Vanilloid receptor (VR) inhibitors for treatment of Human Immunodeficiency Virus (HIV)-mediated pain states/2003	EP 1 493 438 A1	• Bouchon, Axel Dr. 42115 Wuppertal (DE) • Misawa, Keiko Nara, 630-8352 (JP)	Bayer HealthCare AG 51368 Leverkusen (DE)
3	LOW-CONCENTRATION CAPSACN PATCH AND METHODS FOR TREATING NEUROPATHC PAN/2006	US 20060222690A1	Keith R. Bley, Mountain View, CA	MORRISON & FOERSTER LLP 7SS PAGE MILL RD PALO ALTO, CA 94304-1018 (US).
4	USE OF PRODRUGS OF GABAB AGONISTS FORTREATING NEUROPATHIC AND MUSCULOSKELETAL PAIN/2009	US 200901 18365A1	Joseph C. Benson, III, San Jose, CA (US); Peter A. Virsik, Portola Valley, CA (US); Daniel M. Canafax, Half Moon Bay, CA (US)	DORSEY & WHITNEY, LLP INTELLECTUAL PROPERTY DEPARTMENT 370 SEVENTEENTH STREET, SUITE 4700 DENVER, CO 80202-5647 (US)
5	DRUGS ASWELL AS THER PRODUCTION AND USE IN THE TREATMENT OF PAN-ASSOCATED NEUROPATHES/2009	US 2009.0162421A1	Gerd GEISSLINGER, Bad Soden (DE); IrmgardTegeder, Frankfurt (DE)	FOLEY AND LARDNER LLP SUTESOO 3OOOK STREET NW WASHINGTON, DC 20007 (US)
6	TREATMENT OF AIDS DEMENTIA, MYELOPATHY, PERIPHERAL NEUROPATHY, AND VISION LOSS/1992	WO1992003137A1	Stuart A. Lipton	The Children's Medical Center Corporation
7	DRUGS ASWELL AS THER PRODUCTION AND USE IN THE TREATMENT OF PAN-ASSOCATED NEUROPATHES/2009	US 2009.0162421A1	Gerd GEISSLINGER, Bad Soden (DE); IrmgardTegeder, Frankfurt (DE)	FOLEY AND LARDNER LLP SUTESOO 3OOOK STREET NW WASHINGTON, DC 20007 (US)

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8	HISTAMINE H3 INVERSEAGONISTS AND ANTAGONSTS AND METHODS OF USE THEREOF/2011	USOO8063 032B2	Milan Chytil, Clinton, MA (US); Qun Kevin Fang, Wellesley, MA (US); Kerry L. Spear, Concord, MA (US)	Sunovion Pharmaceuticals Inc.,
9	PHARMACEUTICAL FOR ORAL DELIVERY COMPRISING MGBG AND METHODS OF TREATING DISEASE/2011	WO 2011/009039 A2	MCKEARN, John [US/US]; 863 Mitten Road, Suite 101, Burlingame, CA 94010 (US). BLITZER, Jeremy [US/US]; 863 Mitten Road, Suite 101, Burlingame, CA 94010 (US).	PATHOLOGICA LLC [US/US]; 863 Mitten Road.
10	ORAL ADMINISTRATION OF |2-(8,9-DIOXO-2,6-DIAZABICYCLO5.2.0 NON-1(7)-EN-2-YL)ALKYL PHOSPHONIC ACID AND DERIVATIVES/2005	US 2005O142192A1	Eric J. Benjamin, Jamestown, NC (US); William F. Cloud, Garnerville, NY (US); Muhammad Ashraf, Elmwood Park, NJ (US); Mohammed Islam, Harriman, NY (US); Michael R. Brandt, Flemington, NJ (US); Gerald F. Tremblay, Lansdale, PA (US)	WOODCOCKWASHIBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103 (US)
11	NEUROPROTECTIVE SYNERGY OF ERYTHROPOETIN AND INSULIN-LIKE GROWTH FACTOR/2004	US 20040092444A1	Murat Digicaylioglu, San Diego, CA (US); Stuart A. Lipton, Rancho Santa Fe, CA (US)	Cathryn Campbell McDERMOTT, WILL & EMERY Suite 700 4370 La Jolla Village Drive San Diego, CA 92122 (US)
12	FUSED HETEROCYCLIC INHIBITORS OF D-AMNO ACID OXDASE/2008	US 2008.0058395A1	Michele L. R. Heffernan, Worcester, MA (US); James M. Dorsey, Durham, NC (US); Qun Kevin Fang, Wellesley, MA (US); Robert J. Foglesong, Durham, NC (US): Seth C. Hopkins, Clinton, MA (US); Michael L. Jones, Chapel Hill, NC (US); Steven W. Jones, Milford, MA (US); Cyprian O. Ogbu, Durham, NC (US); Joe B. Perales JR. Durham, NC (US); Mustapha Soukri, Raleigh, NC (US); Kerry L. Spear, Concord, MA (US); Mark A. Varney, Laguna Niguel, CA (US)	MORGAN, LEWIS & BOCKIUS LLP (SF) 2 PALO ALTO SQUARE 3000 El Camino Real, Suite 700 PALO ALTO, CA 94.306 (US)
13	PHENYL SUBSTITUTED CYCLOALKYLAMINES AS MONOAMINE REUPTAKE INHIBITORS/2009	US 20090005456A1	Liming Shao, Lincoln, MA (US); FengjiangWang, Northborough, MA (US); Scott Christopher Malcolm, Southborough, MA (US); Michael Charles Hewitt, Somerville, MA (US); Jianguo Ma, Natick, MA (US); Seth Ribe,	MORGAN, LEWIS & BOCKIUS LLP (SF) One Market, Spear Street Tower, Suite 2800 San Francisco, CA 94105 (US)

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			Worcester, MA (US); Mark A. Varney, Laguna Nigel, CA (US); Una Campbell, Marlborough, MA (US); Sharon Rae Engel, Hudson, MA (US); Larry Wendell Hardy, Sturbridge, MA (US); Patrick Koch, Marlborough, MA (US); Rudy Schreiber, Watertown, MA (US); Kerry L. Spear, Concord, MA (US)	
14	FLUORO-SUBSTITUTED INHIBITORS OF D-AMNO ACID OXDASE/2008	US 2008.0004327A1	Michele L. R. Heffernan, Worcester, MA (US); Robert J. Foglesong, Durham, NC (US): Seth C. Hopkins, Clinton, MA (US); Mustapha Soukri, Raleigh, NC (US); Steven W. Jones, Milford, MA (US); Kerry L. Spear, Concord, MA (US); Mark A. Varney, Laguna Niguel, CA (US)	MORGAN, LEWIS & BOCKIUS LLP (SF) 2 PALO ALTO SQUARE 3000 El Camino Real, Suite 700 PALO ALTO, CA 94.306 (US)
15	SYSTEMICALLY AND LOCALLY ADMINISTERED CELLS FOR NEUROPATHIC PAIN/2010	US 20100159025A1	Brian C. Kramer, Plainfield, NJ (US); Uri Herzberg, Bridgewater, NJ (US)	PATTON BOGGS LLP 8484 WESTPARK DRIVE, SUITE 900 MCLEAN, VA 22102 (US)
16	NONSEDATING C-2 AGONISTS/2006	US007 141597B2	Ken Chow, Newport Coast, CA (US); Todd M. Heidelbaugh, Fountain Valley, CA (US); John E. Donello, Dana Point, CA (US); Daniel W. Gil, Corona Del Mar, CA (US)	Allergan, Inc., Irvine, CA (US)
17	METHODS AND COMPOSITIONS FOR THE TREATMENT OF NEUROPATHIES AND RELATED DSORDERS/2007	US 200700.82939A1	Arnold S. Lippa, Ridgewood, NJ (US); Phil Skolnick, Edgewater, NJ (US); Anthony Basile, Hoboken, NJ (US); Zhengming Chen, Belle Meade, NJ (US); Joseph W. Epstein, Monroe, NY (US)	BLACKLOWE & GRAHAM PLLC 701 Fifth Avenue - Suite 4800 Seattle, WA 98104 (US)
18	COMPOUNDS FOR TREATING DISORDERS MEDIATED BY METABOTROPIC GLUTAMATE RECEPTOR 5, AND METHODS OF USE THEREOF/2010	WO 2010/114971 Al	BURDI, Douglas [US/US]; 32 College Avenue, Arlington, MA 02474 (US). SPEAR, Kerry, L. [US/US]; 601 Lexington Road, Concord, MA 01742 (US). HARDY, Larry, Wendell [US/US]; 122 River Road, Sturbridge, MA 01566 (US).	INSOGNA, Anthony, M .et al; Jones Day, 222 East 41st. Street, New York, NY 10017-6702 (US).

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