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Review Article

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Aetiology of Neuropathic Pain (NP) Along with Role of Gabapentinoids Like Pregabalin and Gabapentin in Treating the Excruciating Pain Besides Other Newer Alternatives-a Systematic Review

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Abstract

Neuropathic pain (NP) by definition is a problem that involves the somatosensory system either as a manifestation as disease or as a lesion. Lot of differing causes either of central/peripheral origin can stimulate NP and that might affect life's quality badly. Worldwide prevalence of NP varies from 6.9-10% with spinal cord injury (SCI) explaining 40% of them. The 2nd commonest cause is diabetic peripheral neuropathy (DPN) that accounts for 22-28% of type 2 diabetes mellitus (T2DM). After having reviewed thoroughly how to manage diabetic neuropathic pain here we decided to conduct a systematic review on varying causes of NP and the role of gabapentenoids in managing the excruciating pain. Besides newer opioid analogues not having addictive potential like fentanyl matrix with its availability in intradermal formulations, delta opioid receptor agonist BBI-11008, an innovative analog N-(1-benzylpiperidin-4-yl)-4-fluorobenzamide (LMH2), that is like haloperidol, along with advantages of Gabapentin-ER as well as therapy of trigeminal neuralgia with anticonvulsants like carbamazepine and use in Immunotherapy utilizing 14,18 anti GD2 antibody (ch14.18) associated excruciating pain and in Meralgia paraesthetica (MP) is discussed besides alternative therapies when gabapentenoids fail.

Keywords: Neuropathic Pain (NP); Spinal Cord Injury (SCI); Diabetic Peripheral Neuropathy (DPN); Gabapentenoids; Fentanyl Matrix; BBI-11008; LMH2; Meralgia Paraesthetica (MP)

Introduction

Neuropathic pain (NP) by definition is a problem that involves the somatosensory system either as a manifestation as disease or as a lesion [1, 2]. Lot of differing causes either of central/peripheral origin can stimulate NP and that might affect life's quality badly [3]. Worldwide prevalence of NP varies from 6.9-10% with spinal cord injury (SCI) explaining 40% of them [4, 5]. The 2nd commonest cause is diabetic peripheral neuropathy (DPN) that accounts for 22-28% of type 2 diabetes mellitus (T2DM) subjects [6-8]. Recently we reviewed how to tackle excruciating NP in case of (T2DM). Here we decided to review other causes of Neuropathic pain (NP) along with response to gabapentinoids and if fails other modes of therapy.

Methods

We used the search engine Pubmed, utilizing MeSH terms, Neuropathic pain (NP); gabapentinoids; Pregabalin; gabapentin; mode of action; post amputation pain; opioids; fentanyl; corticosteroid; post herpetic neuralgia.

Results and Discussion

We found a total of 8661 articles out of which we selected 73 articles for this review. No meta-analysis was done.

Role of Gabapentinoids in Neuropathic pain (NP)

1ST line therapy regarding managing NP are gabapentinoids, tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors as well as opioids. Pregabalin and gabapentin represent 2 of the approved gabapentinoids and get prescribed heavily for NP. They are derived from the neurotransmitter that is inhibitory namely gamma-amino butyric acid and bind to the presynaptic α2δ subunit of the voltage–dependent calcium channels that result in decrease in neurotransmitter liberation causing amelioration of post synaptic excitation [9, 10].

Pregabalin got approval for NP syndromes with lot of efficiency in doses varying from 150mg till 600mg daily on the basis of patient's response as well as tolerance. While gabapentin is started at an initial dose of 300mg and gradually titrated to 1800-3600mg daily in three

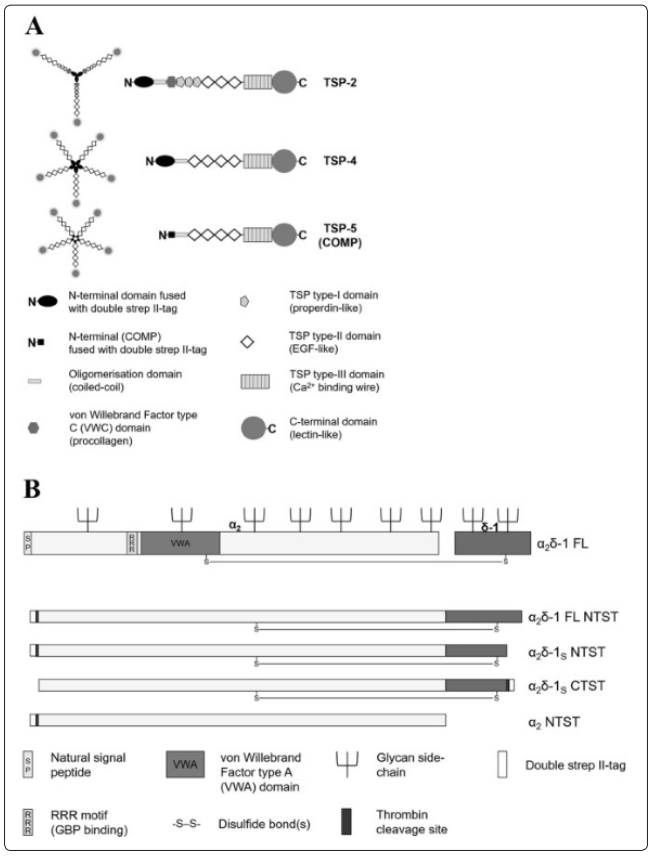
divided doses in case of subjects having normal renal function [10, 11]. Pregabalin requires less frequency of administration with similar efficiency as gabapentin due to >potency, pharmacokinetics that are linear as well as more biological availability [11-13].

Maximum studies done clinically regarding gabapentinoids have documented dizziness, sleepiness as most common dose related side effects that take place in roughly 25%of patients. Other frequent side effects are headache, nervousness, blurring of vision, dryness of mouth pedal oedema increase in weight, constipation, reduced motor coordination as well as ataxia in 1-10% of patients [11, 14, 15].

There are lot of factors that influence difficulty of managing NP, which also include varying diagnostic criteria , response to existing therapies are not sufficient ,with differing efficiency of existing agents. The practices done currently are on the basis of randomized controlled trials (RCT) with clear cut guidelines on doses not being there [12]. Lot of person to person difference occur in the therapeutic effectiveness to gabapentin. Thus Shaheen et al. tried to evaluate the dosages of gabapentinoids being used at present in Pakistani patients presenting with NP and to differentiate the clinical effectiveness as well as tolerance with regards to pain improvement as well as side effects with the utilization of variation in pain score to find out the results of treatment .This was an observational, prospective study carried out in 320 subjects with NP from Aug 16 to mar 18 at Basic Medical Science Institute of Karachi in association with Shifa International Hospital as well as Benazir Bhutto Hospital Islamabad .Demographic data ,therapy associated side effects as well as pain severity was entered on enrollment as well as follow up visits at 2, 4 as well as 8wks. Omission of drug secondary to side effects as well as absence of effectiveness were noted as well. Data following entry got evaluated utilizing SPSS version 22. Mean age of pts was 52.57±12.47 and commonest ethnicity were Punjabi speaking subjects (66%). Diabetic neuropathy (51%) turned out to be the commonest cause and then radicular pain (25%). Average doses of gabapentin and Pregabalin were 470 mg and 114 mg respectively. Average pain score was decreased significantly by gabapentinoids ($p<0.001$). Dizziness drowsiness as well as excessive sleep were common side effects. Frequent dosages of gabapentin and Pregabalin were 300mg daily as well as 75mg daily respectively. Thus concluding that dosages needed of gabapentinoids in NP in Pakistani patients with NP were observed to be effective at lower doses as compared to International recommended doses. Both gabapentin and Pregabalin were identical as far as eradication of pain score although initiation of pain eradicaton was more rapid with Pregabalin. Although Dizziness, drowsiness as well as excessive sleep were usually documented with both gabapentinoids, blurring of vision, ataxia as well as increase in weight was seen only with Pregabalin usage. Side effects are common with gabapentinoids in that makes it essential in going back low doses or shifting to other drugs for pain eradication [16].

Mechanism of Action of Gabapentinoids

Further as is known that α2δ-1 subunit of the voltage–dependent calcium channels binds to gabapentin and Pregabalin that is responsible for bringing about the analgesic action of these drugs against NP. Extra cellular matrix (ECM) proteins from the thrombospondin (TSP) have been found to be the ligands of α2δ-1 in the CNS. This interaction was observed to be key for excitatory synaptogenesis as well as neuronal sensitization that in turn gets inhibited by gabapentin, that pointed to a role in pathogenesis of NP. El-Awaad etal showed direct TSP/ α2δ interaction utilizing an ELISA–style ligand binding assay. Their results demonstrated that full-length pentametric TSP-4, but neither TSP-5/COMP of the pentamer forming subgroup B nor TSP-2 of the trimer forming subgroup-A directly interacted with a soluble variant α2δ-1(α2δ-1S). Intriguingly, this action was not inhibited by gabapentin at a molecular level and was not picked up on the surface of HEK293-EBNA cells that overexpressed α2δ-1 protein. These data give biochemical proof which gives a particular role of TSP-4, of the TSP's in effecting the binding to neuronal α2δ-1 and pointed that gabapentin does not directly target TSP/ α2δ 1 interaction for amelioration of NP (Figure1) [17].



Courtesy ref no-17. Schematic presentation of the structures of the recombinant proteins generated in this study. (A) Domain structure and oligomerisation state of the generated recombinant full-length TSP-2 (trimer), TSP-4 and COMP (pentamers). Schematic representation adapted by permission from Springer Nature, Cell Mol Life Sci, Structures of thrombospondins, Carlson, C. B., Lawler, J. & Mosher, D. F., Copyright (2008). All recombinant TSPs have been expressed with an N-terminal double strep II-tag and contain glycan side-chains which are not shown for reasons of clarity. (B) Structure of α2δ-1 FL protein (adapted from Cell 139, Eroglu, Ç. et al., Gabapentin receptor αδ2δ-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis, 380–392, Copyright (2009), with permission from Elsevier7) and simplified depiction of the derived non-proteolytically processed α2δ-1 mutants generated in this study. The RRR motif, the von Willebrand Factor type A domain, and the glycan side-chains are not shown in the α2δ-1 mutants for reasons of clarity.

Recently Davari etal. Conducted a systematic review and meta-analysis for evaluation of gabapentin and Pregabalin in the therapy of NP secondary to SCI. 8 studies got included after search. Meta-analysis of Pregabalin vs placebo revealed that Pregabalin was efficacious for NP (standardized mean difference [SMD] =-0.40; 95%ci:-0.78,-0.01, anxiety (MD=-0.68; 95%CI-0.77,-0.59) depression (mean difference [MD] =-0.99;95% CI:-1.08,-0.89) and sleep interference (MD=-1.08;95%CI-1.13,-1.02). Similarly gabapentin had >efficacy than placebo for decreasing pain. No significant variation between the 2 agents for omitting the drug due to side effects (risk ratio-3.00; 95%CI: 0.81, 11.15). Thus both gabapentin and Pregabalin had efficacy vs placebo in reducing NP secondary to SCI. Further no significant variation in the 2 drugs for reducing pain as well as side effects was observed [18].

Role in Post Amputation Pain (Pap) of Gabapentin ER

The post amputation pain (PAP) by definition is pain originating in a part that has been surgically amputated following amputation, and continues for a lot of months following amputation and where other reasons for pain have been eliminated [19, 20]. Basically PAP is thought to be a Neuropathic kind of pain, that starts in central as well as peripheral NS [21-23]. PAP has come out to be the main anticipator of patients quality of life (Qol) after surgery [24]. Its incidence documented is 33-80% [25, 26]. Lot of cost burden is there, since managing pain puts maximum financial burden on qol with cost factor in terms of long time nature of PAP [25-29]. Further cost, besides direct effect on patients health and enhanced call regarding health care resources, but further has indirect impact on patients family and those taking care of pts, due [30, 31]. But effectiveness of available therapies at present are queried, with the less satisfaction rates documented literature wise [32, 33]. As PAP is believed to be a Neuropathic kind of pain, particular focus is on utilizing gabapentin for avoiding and treating pain [34]. But use of gabapentin for treating pain for PAP is little in view of its side effects, especially at starting the therapy that is the reason why lot of patients give up this therapy in initial phases of start [35]. Adverse effects of gabapentin are secondary to short half life => repeated dosages at small periods with absorption that can't be anticipated from the gastrointestinal tract (GIT), resulting in blood levels that are not consistent in blood with tough to titrate its levels, A new formulation of gabapentin called gastroretentive or extended release (ER) gabapentin has been formed to aid in slow absorption rate from the gut ,that would enhance tolerance of Adverse effect s without influencing effectiveness [34]. Gabapentin ER has been deeply examined for therapy of postherpetic neuralgia. It has demonstrated to be an efficacious analgesic, with lower rate of side effects as compared to gabapentin immediate release (IR) [37, 38]. Thus Kneziev et al. conducted an open label pilot study where 16 patients having post amputation pain [n=8 in Gabapentin ER group as well as Gabapentin –naïve group n=8]. Patients from both groups, Gabapentin ER group as well as Gabapentin–naïve group obtained significant pain reduction that was maintained throughout duration of treatment. The pain scores at rest reduced in both Gabapentin-experienced as well as Gabapentin naïve group from 5.88±1.36 and 4.88±2.95 to 1.88±0.99 and 1.38±1.51 respectively. An average degree of pain overcome in percentage with Gabapentin ER was found to be of significance ($p<0.01$)) that were followed uptill 8wks of treatment in Gabapentin-experienced (81.25±16.42%) as well as Gabapentin naïve group (85±17.73%) as compared to baseline for Gabapentin-experienced(31.25±29)% as well as Gabapentin naïve group (36.25±34.2%) respectively. Gabapentin-experienced as well as Gabapentin naïve group presented no significance regarding total satisfaction obtained through therapy (79.14±10.47 and 83.3±20.82), ease of therapy (73.78±19.04 as well as 90.44±11.66), and efficacy of therapy (72.6±10.1and79.73±11.6). Only finding that had statistical significance between Gabapentin-experienced as well as Gabapentin naïve group was the separation in side effect tolerance (65.78±10.36and85.8±10.14,$p<0.01$). Thus they concluded that Gabapentin ER once daily intake displayed significance benefit in terms of pain degree as well as functioning with no separation observed in Gabapentin-experienced as well as Gabapentin naïve subjects [39].

Comparison of Gabapentinoids VS Fentanyl Matrix –Dermal in NP

Neuropathic pain (NP) by definition is pain caused due to a lesion or disease of the somatosensory system [40]. Different aetiologies explain it, like lumbar radiculopathy, that is usually the etiology of low back ache with sciatica i.e one of the commonest systems found in primary care settings.

In view of this commonness, different kinds of medicines have been used for therapy of NP. Gabapentin basically is an anticonvulsant which is prescribed usually for NP in view of its effectiveness in NP secondary to diabetic neuropathy, post herpetic neuraligia, and other Neuropathic problems as shown in variety of randomized controlled trials (RCT's) [41].

Opioids that are supposed to be most efficacious broad spectrum analgesic for acute pain have been utilized for therapy of acute pain despite the controversy over their effectiveness as well as safety [12, 42-45]. Like fentanyl has marked potency as compared to morphine that got manufactured initially in 1950's [41]. Earlier it got utilized for intravenous anaesthesia as well as analgesia, but now it is getting written more for chronic pain in view of the recent formation of transdermal formulation. Patch of fentanyl, that has safety In cases of renal deficiency, it being a good drug for patients who can't orally digest fentanyl, with lesser chances of constipation as compared to conventional opioids.

Different studies have documented the effectiveness of different medicines for NP, but Gabapentin and fentanyl have not been compared regarding pain relief from lumbar radiculopathy. Thus Hwang et al. tried to concentrate on the safety as well as ease of transdermal fentanyl planned a randomized controlled trial (RCT) for this comparison in a noncancer setting. They analyzed the relative effectiveness as well as safety of fentanyl matrix as well as Gabapentin for treating chronic NP that had radicular initation. The design was a randomized blind multicentred parallel group non inferiority trial. 108 patients presenting with moderate to severe pain (≥4 intensity on an 11 point numeric rating scale) got randomly given as fentanyl matrix or Gabapentin in a 56 duration time period. For the primary evaluation, non inferiority of fentanyl matrix treatment got analyzed in association to Gabapentin effectiveness on the basis of pain intensity difference (PID) at 56 days following the 1st dosage of the agents. Secondary endpoints were pain relief, improved functional status (the Korean–Oswestry Disability index (K-ODI), improved depressive symptoms (Korean–Beck Depression Index-K-BDI) among the 28th -56th day and side effects. Evaluation of the primary effectiveness y endpoints confirmed the non inferiority of fentanyl matrix with Gabapentin with no statistically significant difference seen in the PID following 56th day for both groups.

No variation in the K-ODI as well as K-BDI among the 2 groups. Total incidence of atleast one side effect for patients receiving fentanyl matrix (67.3%) was similar to that in Gabapentin (69.6%). Commonest documented side effect for fentanyl matrix treated patients as well as Gabapentin were dizziness (30.8% vs 44.6% respectively), somnolescence (26.9% vs 35.7%) and constipation (15.4% and 17.9%). Thus this study showed that the analgesic action of fentanyl matrix is noninferior as compared to Gabapentin supporting the use of fentanyl matrix as being a safe as well as efficacious therapy for moderate to severe chronic NP. Reg no of trial NCT01127100 [46].

Role in Post Herpetic Neuralgia (PHN)

Commonest chronic side effect of herpes zoster (HZ; shingles) is post herpetic neuralgia (PHN), a persistent NP which occurs following acute HZ infection. HZ is believed to be a significant public health hazard, in view of its enhancing incidence in addition to the ageing; population with significant effect on quality of life (Qol), in the acute as well as chronic phases [47, 48]. Further recently HZ correlated with >chances of cerebrovascular (CVS) as well as Cardiac events immediately following acute infection [49].

Varicella zoster virus (VZV), Is a double stranded DNA virus that is the etiological agent for chickenpox, whose activation repeatedly, results in HZ. VZV continues to be dormant within the dorsal root ganglion and on reactivation particularly in adults >50yrs causes unilateral, dermatomal as well as painful skin eruptions [50]. This reactivation of VZV correlates with age associated reduction of cellular immunity to VZV and with dysfunctional cellular immune function [51].

Prior to universal Varicella immunization getting introduced, seroprevalence of VZV was evaluated to be >95% in people >65 yrs over 16 European nations as per a current systematic review, hence many people remain to be at risk for developing HZ [52]. Incidence of HZ escalates with age. Total calculated incidence is 3.4 to 4.82 /1000 person years and escalates up to 11/1000 person years in patients >80yrs [53].

Risks of developing PHN in persons with HZ varies from 5->30% but differences of opinion exist regarding the incidence as well as prevalence of PHN since no definition that is agreed on universally is present [54]. Hence as per a comprehensive review the incidence of PHN documented was 3.9 to 42/100,000 person years [55]. Definition in earlier studies of PHN was as per the degree of pain severity (≥3or4 on a 10point Likert scale) or duration (pain persisting for 30, 90; 120 or 180days) [56, 57]. Main risk factors are constituted by older age, >acute pain, >widespread rash, presence of prodromal pain as well as ophthalmic involvement [54].

Pain is usually told to be constant or intermittent as well as burning, aching throbbing, stabbing or shooting. Certain patients also document allodynia, hyperalgesia as well as dysaesthesia [58]. This pain that is very long persisting as well as debilitating that might remain for months to years with it being refractory to pharmacological treatment [54].

PHN has a derogatory effect on physical, social, functional as well as psychological domains as well as related with a lot of burden on pts, caregivers, the health care system as well as employees [48, 53].

Many treatments have been offered for preventing PHN that are antivirals, amitrytaline as well as pregabalin, interventional actions like epidural as well as sympathetic nerve blocks, VZV vaccination and complementary as well as alternate therapies like acupuncture as well as electrical Nerve stimulation. A Cochrane systematic review documented that antivirals like acyclovir might reduce the degree of acute HZ pain at 1mth as compared to placebo but didn't have any action of avoiding PHN [58]. Same review emphasized the requirement of > number of studies of valacyclovir and famciclovir and of separate group of patients. Another study documented that corticosteroids administration in the acute phase of HZ did not avoid PHN [59, 60]. Some proof is there for amitrytalline (25mg/day x 3mths) might reduce the incidence of PHN though >work is needed for corroborating the results of the lone study [61].

HZ vaccine is the only accepted method for preventing PHN, although the efficacy of live attenuated vaccine appears to reduce over time [56, 62]. A recombinant zoster vaccine (Zostavax), recently obtained approval for adults ≥50yrs old, with this new vaccine appearing to have > effectiveness for avoiding HZ as well as PHN [63].

Gabapentin is an anticonvulsant originally formed and approved as an additional therapy for treating partial seizures, usually utilized in treating NP [64]. It is an analogue of GABA as well as binds to the α2- δ site of the voltage– dependent calcium channels and hence decreasing neuromitter liberation [65]. An earlier study documented that Gabapentin decreases acute herpetic pain as well as delayed post herpetic pain in mice [65]. Human studies showed Gabapentin was of use for the therapy of chronic NP and may also decrease allodynia as well as hyperalgesia [66]. The European consensus based guidelines on HZ management advocates that Gabapentin be added to analgesics for treating HZ infection if moderate or severe pain is existing [67].

Buillete et al. tried to find the effectiveness of a 5wk course of Gabapentin on acute herpetic pain as well as on the avoidance of PHN at 12wks in patients having HZ. They conducted a randomized, placebo controlled trial in 17 primary care health centres in Madrid, Spain. All patients were >50yrs, coming with HZ within 72h of rash initiation ,having moderate–severe pain ((≥4 on a 10point visual analogue scale [VAS]) 98 pts received valaciclovir for 7days as well as analgesia if required. Treatment period was 5wks, fb 7wks of Follow up. Gabapentin was started at 300mg/d and titrated slowly to a maximum 1800mg/day. Basic outcome measure was pain at 12 wks.75% finished the study, 33 in the Gabapentin group and 42 in control group. Totally 18.2% of pts in the Gabapentin grp and 9.5% in the control grp documented pain of 4 or >points on a 10 points VAS. Pts receiving Gabapentin documented worst health associated qol and bad sleep quality. 3 patients stopped the trial in view of side effects of Gabapentin. Thus concluding that adding Gabapentin to the routine therapy of HZ within 72h of rash onset gave no significant benefit from acute herpetic pain or avoid PHN. Trial Reg no-ISRCTN79871784 [68].

Role in Trigeminal Neuralgia

The trigeminal nerve (V) is the 5th and biggest of all cranial nerves and it causes direct sensory stimuli which start from the craniofascial are, There are 3 branches of the nerve-ophthalmic (V1), maxillary (V2) awa mandibular (V3), with their cell bodies present in the trigeminal ganglia where they connect with 2nd order neurons in the trigeminal brainstem sensory nuclear complex (VBSNC). Ascending group through the trigeminothalamic tract emit information to the

thalamus along with other brain areas that interpret sensory input. 1 of the commonest type of craniofascial pain is trigeminal neuralgia (TN). TN starts as a sudden, short, severe facial pain attack in 1 or >branches of Vth nerve, resulting in marked decrease in Qol of the patients afflicted. TN causes can be idiopathic, classic as well as secondary. Classic TN correlates with neurovascular compression of the trigeminal nerve root entry area, that can cause demyelination as well as dysregulation of voltage –gated sodium channels (VGSC) expression in the membrane. These changes might cause pain attacks in TN patients. Carbamazepine (CBZ), the antieleptic drug as well as oxcarbazepine (OXC) are the 1st line pharmacological therapy for TN. Mode of action is manipulation of VGSC, causing a reduction in neuronal activity. Though CBZ as well as OXC are the 1st line of therapy other drugs might be used for pain control. Of these, Gabapentin, Pregabalin, lamotrigine and phenytoin, baclofen and botulinium toxin type A might be given with CBZ as well as OXC to get asynergism. Newer pharmacological alternatives are being evaluated like active metabolites of OXC, eslicarbazepine, as well as new Nav 1.7 blocker vixotrigine that Gambeta et al reviewed [69].

Role of Δ Selective Opioid Receptor Agonist BBI-11008

Stevenson et al. tried to evaluate the behavioral pharmacology of the mixed action δ selective (78:1) opioid receptor agonist BBI-11008. They tested the present glycopeptides candidate in assays for antinociception (acute, inflammatory, as well as NP–like problems) as well as adverse event endpoints (like respiratory depression as well as drug self intake) They observed BBI-11008 posessed 78 times more affinity for the δ opioid receptor as compared to μ opioid receptor and no binding to kappa opioid receptor was seen. BBI-11008 (3.2-100;10-32mg kg^{-1},i.v) as well as morphine (1-10;1-3.2mg kg^{-1}) gave antinociceptive as well as antiallodynic actions in assays of acute thermal nociception as well as complete Freund's adjuvant (CFA)-induced inflammatory pain, with BBI-11008 having lesser potency as compared to morphine in both assays. BBI-11008(1-18 mg kg^{-1}, i.v) had similar effectiveness as Gabapentin (10-56 mg kg^{-1}.i.v.) in a spinal nerve ligation (SNL) model of NP. In respiratory assays with escalating % CO_2 exposure, BBI-11008 got an earlier enhancement (32mgkg^{-1}, s.c.) and later reduction (56mg kg^{-1}.s.c.) in minute volume (MV) while morphine (3.2-32 mg kg^{-1}, s.c.) lead to dose dependent reduction in. MV. In drug self intake BBI-11008 did not maintain self intake at any of doses. Thus the data pointed that glycopeptides drug candidate has broad spectrum antinociceptive as well as antiallodynic actions in a broad categories of pain like problems. As compared to morphine or fentanyl the profile of BBI-11008 in the respiration as well as drug self intake points that BBI-11008 might have < adverse effects in degree. Repeated checking of this agent is needed [70].

Role of Haloperidol like LMH2

Haloperidol represents a neuroleptic drug having great affinity for the epsilon receptor (σ1 R), that acts like an antagonist which reduces NP, but possesses CNS adverse actions. Deciga-Campos et al. detailed the designing as well as manufacture of an innovative analog N-(1-benzylpiperidin-4-yl)-4-fluorobenzamide (LMH2), that got hyperalgesic as well as allodynic actions in rats having neuropathy stimulated by chronic constriction injury (CCI) of the sciatic nerve, having> activity as compared to Gabapentin. They designed LMH2 as a Haloperidol analogue. Its structure was characterized utilizing spectroscopic (^{1}H and ^{13}C NMR) as well as spectroscopic mass (electronic impact) techniques. Moreover in siilico projections of pharmacokinetics, pharmacodynamics as well as toxicological characteristics got retrieved that had encouraging results. A competitive binding assay utilizing radioligands were used for analyzing the in vitro affinity for epsilon 1 R, while in an in vitro binding assay, having a KI=6.0NM as well as high σ 1 R/σ 2 R selectivity ratio. Molecular docking studies were conducted to find the binding energy as well as to evaluate LMH2 protein interactions .Through am in silico Pharmacological consensus evaluation LMH2 was thought to be safe regarding in vivo analyses. Hence LMH2 posessed dose dependent antiallodynic as well as antihyperalgesic activities, and its effectiveness was comparable with that of Gabapentin, but it had twice the potency >than this drug. Thus LMH2 intake gives antiallodynic as well as antihyperalgesic activities by antagonizing epsilon 1R, pointing a potential use as analgesic drug for Neuropathic pain [71].

Role in NP due to Immunotherapy Utilizing 14, 18 Anti GD2 Antibody (ch14.18)

Immunotherapy utilizing 14, 18 anti GD2 antibody (ch14.18) correlates with excruciating NP. Variety of analgesic therapies have been used, but pain management is tough with adverse effects like desaturation, bradycardia as well as hypotension have been documented. Berotolizio etal, retrospectively evaluated the efficiency of a multimodal regimen having Gabapentin, ketamine as well as morphine in regulating pain during ch14.18 chemotherapy. In their cohort, pain was low, desaturation, as well as hypotension were very less with no bradycardia episode documented .Morphine intake was similar to other studies. Their results suggested that this regimen was a good analgesic option in children undergoing ch14.18 infusion [72].

Role in Meralgia Paraesthetica (MP)

Meralgia paraesthetica (MP) is a painful mononeuropathy of the lateral femoral cutaneous nerve. It is usually idiopathic and gets treated with drugs utilized for NP like Pregabalin, Gabapentin and amitrytalline. Elavarasai etal, tried to study retrospectively the efficacy of triamcinolone acetonide on drug refractory MP.8 subjects got therapy with local injections of triamcinolone. Follow up for 4 months to 54mths demonstrated significant symptomatic benefit and 6patients had complete improvement, with all patients documenting > 50% relief. Thus concluding that triamcinolone acetonide injection locally appears to be an efficacious as well as safe therapy for refractory MP. They have planned a RCT for effectiveness as well as safety [73].

Conclusions

Thus variety of NP exist with varying etiology from SCI, T2DM–Diabetic peripheral neuropathy, being the commonest. Others causes are post herpetic neuralgia, post amputation pain. In most of these gabapentinoids are effective in relieving pain. In case where patients can't tolerate side effects like drowsiness, somnolescence in those Gabapentin ER or gastroretentive Gabapentin might be utilized. Other agents being tried are fentanyl matrix intra dermally, newer delta analog BBI-11008or newer haloperidol like agent LMH2. Management of trigeminal neuralgia includes Gabapentin with carbamazepine or other combinations. Meralgia paraesthetica that is refractory to all other drugs including gabapentinoids. Corticosteroids, need injection of triamcinolone that relieves pain.

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