Review

First line symptomatic therapy for painful diabetic neuropathy: A tricyclic antidepressant or gabapentin?

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Abstract

Diabetes is a high prevalence disease leading among others to painful diabetic neuropathy (PDN). Tricyclic antidepressants (TCA) were considered as first line therapy for symptomatic pain therapy. While their efficacy is reasonably well established, their adverse drug reaction (ADR) profile limits their usefulness. Third generation antidepressants like venlafaxine could overcome these limitations but data concerning their efficacy are limited. Among clinicians a new therapeutic trend is occurring: gabapentin, a drug initially marketed as an antiepileptic, is becoming increasingly popular as the first line therapy for PDN. Gabapentin is a ligand for the alpha$_2$/delta modulatory subunit of calcium channels, thus decreasing intracellular calcium availability. Initial data on the effectiveness of gabapentin in PDN indicates an efficacy comparable with secondary amine TCAs. The reason for gabapentin's popularity is the benign ADR profile and the lack of relevant drug-drug or drug-food interactions.

Key words: *Painful diabetic neuropathy, tricyclic antidepressants (TCA),symptomatic pain therapy, gabapentin*

Introduction

Diabetes affects over 15 million people in the United States, or 5.9 percent of the population. While an estimated 10 million people have been diagnosed, 5 million are not aware that they have the disease. The reported prevalence varies but generally seems to be on the rise. The number of Americans with diagnosed diabetes is projected to increase by 165%, from 10 million in 2000 (prevalence of 4.0%) to 29 million in 2050 (prevalence of 7.2%).[1] For Ontario, Canada, the all-age prevalence increased from 3.2% in 1993 to 4.5% in 1998 (6.1% in adults); however, the incidence remained stable.[2] Data from a city in India shows a prevalence of known diabetes of 2.9% for all ages and both sexes combined (prevalence 10.5% in those aged ≥ 40 years).[3] For Phillipino-Americans aged 20-74 years, overall prevalence was estimated to be 16.1%.[4] Using a very conservative approach and assuming a worldwide all-ages prevalence of 3%, the total number of diabetic patients can be estimated as being over 150 million.

The prevalence of diabetic neuropathy varies from 10% within 1 year of diagnosis to 50% in patients having the disease for more than 25 years.[5] As such the numbers for patients having diabetic neuropathy range from 15-75 million. A minority, probably one order of magnitude lower, will develop Painful Diabetic Neuropathy (PDN). Treatment

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of diabetic neuropathy is multi-layered, including aetiology driven causal treatment, elimination of risk factors, and symptomatic therapy (i.e., chronic pain therapy).

The focus of this review is the two top contenders for the title "drug of choice" for symptomatic pharmacological therapy in PDN: antidepressants and gabapentin. After reviewing pharmacokinetic, pharmacodynamic, and clinical efficacy aspects of the two drug classes, an attempt is made to address the question which drug, a tricyclic antidepressant or gabapentin, is the drug of choice for PND?

Pain

In a very simplified model the nociceptive system consists of an afferent three neuron pathway (peripheral nociceptor → dorsal horn → ventroposterolateral thalamus → sensory post-central cortex) and two efferent modulatory (inhibitory) pathways to the spinal cord. The first inhibitory pathway originates at the level of midbrain in the periaqueductal gray matter and has serotonin (5-HT) as the major neurotransmitter. The second originates at the level of the locus ceruleus in the medulla and has norepinephrine (NE) as the major neurotransmitter.[6]

Nociceptor pain (originating from peripheral receptors reacting to noxious stimuli) is teleologically meaningful having the purpose of alarming the body of acute impending damage. Nociceptor pain is clinically controlled with cyclooxygenase (COX) inhibitors and/or opioids. The analgesic effect of cyclooxygenase (COX) inhibitors is related to their ability to mainly decrease peripheral prostaglandin production; however, their clinical usefulness is limited to treatment of mild to moderate pain. Opioids exert their analgesic effect by interacting with endogenous opioid-peptide receptors of different subclasses located at spinal and supra-spinal level.

Neuropathic pain is a symptom of nervous system damage. It is generated by the nervous system itself without input from nociceptors. It serves no meaningful purpose and it can be thought of as a sign of insufficiency of the efferent inhibitory component of the nociceptive system. While complex and not well understood, the mechanism of neuropathic pain involves changes at both peripheral and central levels. In the periphery, there is an upregulation of sodium channels in areas of axonal damage leading to decreased threshold and ectopic discharges. This appears to be the molecular correlate of peripheral sensitization.

On the spinal level, a plethora of excitatory neurotransmitters is released so that the inhibitory neurotransmitters gamma-amino-butyric-acid (GABA) and glycine are overpowered.[6,7,8] Excitatory neurotransmitters interact with N-methyl-D-aspartate (NMDA) and neurokinin (NK-1) receptors, the net result being an increased entry of calcium into the cell and potentiation of calcium mediated effects. This appears to be the molecular correlate of central sensitization.

Neuropathic pain is resistant to COX inhibitors and/or opioids.[9,10] According to the model presented, a number of drug classes have potential therapeutic utility in the treatment of neuropathic pain:

- Sodium channel blockers (opposing mainly peripheral sensitization)
- Calcium channel blockers (opposing mainly central sensitization)
- N-methyl-D-aspartate (NMDA) and neurokinin (NK-1) receptor

blockers (opposing mainly central sensitization)
- GABA agonists
- Serotonin (5-HT) and/or norepinephrine (NE) re-uptake inhibitors (potentiating the inhibitory component of the nociceptive system)

Neurotransmitter transporter inhibitors (5-HT and/or NE reuptake inhibitors)

More than 20 members have been identified in the neurotransmitter transporter family. These include the cell surface re-uptake mechanisms for monoamine and amino acid neurotransmitters and vesicular transporter mechanisms involved in neurotransmitter storage. The only clinically used compound to emerge so far from research on amino acid transporters is the antiepileptic drug, Tiagabine, a GABA uptake inhibitor. Drugs increasing the synaptic availability of the biogenic amines, norepinephrine (NE) and serotonin (5-HT), however, have been in clinical use in the treatment of depression for more than four decades.[11]

The first generation anti-depressants were all chemically related to carbamazepine, an anticonvulsant drug, sharing with it the tricyclic structure. Thus they are commonly described as tricyclic antidepressants (TCA). Depending on the nitrogen atom in the molecule TCAs can be divided into secondary or tertiary amines, the clinical relevance of that being the differential effect on biogenic amines reuptake. Secondary amines (desipramine) inhibit more the NE reuptake as opposed to tertiary amines (amitriptyline, imipramine, clomipramine) which inhibit NE and 5-HT reuptake to comparable extents. TCAs are often described by pharmacologists as “dirty drugs” the implication being that TCAs are not selective in terms of pharmacodynamic action. In addition to their effects on biogenic amines, they also interfere – as carbamazepine does - with a lot of other targets, such as ionic channels and neurotransmitter receptors, thus explaining the side effects of TCA. The adverse drug reactions (ADR) of TCA include:

- $Histamine_1$ receptor blockage, leading to sedation and weight gain
- Muscarinic receptor blockage, leading to tachycardia, dry mouth, constipation, urinary retention, ocular accommodation disturbances, and memory impairment
- Alpha-adrenergic receptor blockage, leading to vasodilatation, postural hypotension and reflex tachycardia
- Na-channel blockage, leading to quinidine-like cardiac toxicity and seizures
- K-channel blockage, leading to cardiac toxicity (QT – prolongation)
- $Dopamine_2$ receptor blockage, leading to extrapyramidal motor symptoms and an increase in prolactin levels

In addition, postural hypotension often leads to falls and secondary trauma. Furthermore, TCAs have a low therapeutic index, the upper therapeutic drug range being close to the lower toxic range. This, combined with the often-unpredictable pharmacokinetics, make TCAs one of the common causes of drug toxicity. These side effects, while more pronounced with tertiary amines than with secondary ones, are generally the limiting element in the usefulness of

both TCA subgroups. However, low product price is a major advantage of TCAs.

The second generation antidepressants are not related structurally to carbamazepine. In fact, they are structurally very heterogeneous (fluvoxamine/monocyclic, fluoxetine/ bicyclic, sertralin and citalopram/tricyclic, paroxetine /tetracyclic), and the common ground is their pharmacodynamic effect- selective serotonin reuptake inhibition (SSRI). Compared to TCAs, these are pharmacodynamically much "cleaner" drugs; however, they interfere with the hepatic metabolism of coadministered drugs via the inhibition of cytochrome P450 isoenzymes (CYP). CYP2D6 (debrisoquine hydroxylase) is inhibited by SSRIs paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram, and fluvoxamine (in the order of decreasing potency). In addition, fluvoxamine inhibits most, if not all, known CYP isoforms.[12]

The third generation anti-depressants are also structurally and pharmaco-dynamically heterogeneous. The "xetins" reboxetine and atomexetine are selective reuptake inhibitors of norepinephrine and, with analogy to the SSRI group of antidepressants, could be called NESRI.

Nefazadone is a SSRI with additional 5-HT_2- receptor blocking properties. The theoretical advantage of an inhibitory substance at this particular 5-HT receptor subtype is the possibility of a reduced incidence of sexual dysfunction, which is one of the major side effects of SSRI. Mirtazapine is a central presynaptic $alpha_2$ receptor blocker (clonidine is a postsynaptic $alpha_2$ receptor agonist), resulting in a net increase in NE and 5-HT release. In addition, mirtazapine blocks 5-HT_2-receptors (reduced incidence of sexual dysfunction) and 5-HT_3-receptors (reduced incidence on nausea and vomiting). The beauty of mirtazapine lies in its novel pharmacodynamic concept. Unfortunately the usefulness of this drug is limited by its side effects, mainly sedation and weight gain ($histamine_1$ receptor block), as well as antimuscarinic effects (dry mouth and urine retention).[13,14]

The most interesting third generation antidepressant in the context of this review is venlafaxine. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV) are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. *In vitro* studies have demonstrated that venlafaxine and ODV do not possess any significant affinity for muscarinic, H_1 histaminergic, or $alpha_1$ adrenergic receptors. Although venlafaxine is a bicyclic compound, one could envision it as a tertiary amine TCA without the side effects (clean tertiary amine TCA). Venlafaxine, and its major active metabolite, O-desmethylvenlafaxine, exhibit linear kinetics with an elimination half-life of 5 and 11 hours. Of the marketed antidepressants, venlafaxine is less commonly involved in clinically important drug interactions. Both *in vitro* and *in vivo* data indicates that venlafaxine either does not inhibit or weakly inhibits the activity of CYP isoenzymes.[15,16]

Use of TCA for PDN

When treating depression one is aware of the time-lag between initiation of therapy and clinical improvement. Although the increase in biogenic amines in the brain occurs immediately after TCA application, weeks go by before the patient feels the improvement. The explanation for this delay is that the

correlate, at cellular level, for the clinical improvement is a change in density and sensitivity of neurotransmitter receptors (up-regulation of $alpha_1$ and $5\text{-}HT_1$ receptors, down-regulation of beta and $5\text{-}HT_2$ receptors) which requires weeks of exposure to TCA. No such adaptive mechanisms are required for the analgesic effect of TCA as this depends directly on the increase in the levels of biogenic amines. Thus, clinical improvements are observed much faster with TCAs (days vs. weeks). In terms of required dose, the analgesic dose is, generally speaking, lower than the antidepressive dose. As Beydoun put it, it is important to "start low and go slow" in increasing the dose towards the effective or maximally tolerated one.[8]

Clinical studies with antidepressants for PDN

The TCAs were tested in a number of clinical trials. Virtually every clinical trial has confirmed this basic result- both tertiary and secondary amines are superior to placebo in which there is a statistical trend favouring tertiary amines over secondary amines, but it rarely reaches statistical significance. The most widely quoted trial by Max[17] was a double blinded, placebo-controlled, cross-over trial comparing the efficacy of a tertiary amine (amitryptiline), a secondary amine (desipramine), and a SSRI (fluoxetine) with a placebo. Amitryptiline was the most effective (NNT≈ 3.3), followed by desipramine (NNT ≈ 5) and fluoxetine (NNT ≈ 14). The percentage of patients reporting an improvement in pain scores (moderate or significant) after correction for placebo effect was 33 for amitryptiline, 20 for desipramine, and 7 for fluoxetine. In another study, Vrethem and colleagues compared the efficacy of amitriptyline to that of maprotiline (a tetracyclic norepinephrine reuptake inhibitor) and a placebo.[18] The percentage of patients reporting an improvement in pain scores after correction for placebo effect was 42 (amitryptiline; NNT ≈ 2.4) and 18 (maprotiline; NNT ≈ 5.5).

Recently, Syndrup and Jensen[19] reviewed the efficacy of pharmacological treatments of neuropathic pain. In diabetic neuropathy, NNT was 1.4 in a study with optimal doses of the tricyclic antidepressant imipramine as compared to 2.4 in other studies on tricyclics. The NNT was 6.7 for selective serotonin reuptake inhibitors, 3.3 for carbamazepine, 10.0 for mexiletine, 3.7 for gabapentin, 1.9 for dextromethorphan, 3.4 for tramadol and levodopa and 5.9 for capsaicin. While this review was criticized on several methodology points it still gives an idea about the relative efficacy of available drugs.[20]

In a further systematic review of antidepressants in neuropathic pain, the NNT for benefit when using TCAs was 3 [95% confidence interval (CI) 2.4 - 4]. Comparisons among different tricyclic antidepressants did not reveal any significant differences.[21]

Data are insufficient to determine whether all tricyclic antidepressants are equally effective. Double blind, placebo controlled, crossover clinical trials have demonstrated the efficacy of the TCAs amitryptiline, imipramine, clomi-pramine, and desipramine.[8] Based on the large body of data available amitriptyline and desipramine are first choice TCAs in treating painful diabetic neuropathy.[22, 23]

The second generation antidepressant fluoxetine was virtually indistinguishable from placebo in the treatment of PDN according to the Max study.[17] In another study[24] the efficacy of imipramine was compared to that of a

SSRI (paroxetine) and to placebo. Both the TCA and the SSRI were effective, however, the TCA was superior to the SSRI. Sindrup et al., further suggest that increasing the paroxetine dose would improve efficacy.[25] Virtually identical conclusions were drawn with respect to citalopram.[26]

Data comparing the third generation drugs with placebo and the TCAs of choice are slowly emerging. The initial data for venlafaxine derived from over 20 patients and presented as case reports are promising.[27,28,29]

A double-blind, placebo-controlled, parallel-group multi-site study presented at the 60th annual meeting of the American Diabetes Association,[30] shows that venlafaxine (Effexor) is effective in reducing pain associated with diabetic neuropathy. In the study, 244 patients of 18 years of age or older with type 1 or type 2 diabetes were randomly assigned to receive treatment with venlafaxine 75 mg, 150-225 mg, or placebo for up to 6 weeks. Venlafaxine 150-225 mg produced significantly greater pain relief compared with placebo. The percentage of patients reporting an improvement in pain scores after correction for placebo effect was 22 (NNR 4.5), a result similar to that of secondary amines. The major advantage of venlafaxine is the benign side effect profile, with the most common adverse effect reported being nausea.

Based on the available studies, it appears that blockade of norepinephrine reuptake is likely to mediate most of the analgesic effects of TCAs in diabetic neuropathy. The contribution of inhibition of serotonin reuptake appears to be less important. It is unclear whether the statistical trend favouring tertiary amines over secondary amines is due to inhibition of serotonin reuptake (more pronounced in tertiary amines) or due to other effects more pronounced in tertiary amines as compared to secondary ones (Na channel block, H_1 receptor block). The efficacy of the available antidepressants for treatment of PDN appears to be:

Tertiary TCAs ≥ secondary TCAs = NESRI (venlafaxine) > SSRI ≥ placebo

Gabapentin (Neurontin®)

Gabapentin was introduced in the early nineties. It is a white crystalline solid, freely soluble in water and both basic and acidic solutions. The chemical structure of gabapentin is derived by addition of a cyclohexyl group to the backbone of gamma-aminobutyric acid (GABA). The molecular weight is 171 while the pKa is 3.7. Oil/water partition coefficient for gabapentin is 10 times higher than for GABA itself, explaining the good CNS penetration.

Absorption from the digestive tract is via a saturatable amino acid transporter (leucine, isoleucine, valine and phenylalanine L-form selective amino acid transporter). As such bioavailability of the drug is not linearly dose dependent- as the dose is increased, bioavailability decreases. Over the recommended dose range, however, the differences in bioavailability are not large. The total gabapentin bioavailability is around 60%. Food affects only minimally the extent and rate of gabapentin absorption. The substance is not bound to plasma proteins to any relevant extent (< 3%), is not metabolized, and elimination is via renal clearance (proportional to creatinine clearance). Dose or application interval adjustments according to creatinine clearance calculated via the Cockroft & Gault formula are necessary. The apparent volume of distribution (Vd) is in the 60 l range, corresponding to the total body

water content. Plasma half-life is around 6-8 h, making tid application of the drug necessary. The aforementioned amino acid transporter is responsible for the high gabapentin concentration in the CNS cytosol as compared to liquor. Liquor gabapentin concentrations are approximatively 1/5th of plasma concentrations.[6] Gabapentin neither induces nor inhibits hepatic enzymes. It also does not exhibit any relevant drug-drug or drug-food interactions.[31]

Pharmacodynamic effects

Due to the structural similarity between gabapentin, GABA and baclofen (a GABA-B receptor agonist in clinical use) it was a foregone conclusion that gabapentin must be a GABA receptor agonist. The reality turned out to be, as always, much more complex, the pharmacodynamic effects of gabapentin being difficult to elucidate. In addition, gabapentin is not converted metabolically to GABA, it is not an inhibitor of the GABA transporter (GABA reuptake) nor an inhibitor of GABA degradation. Gabapentin does not exhibit affinity for a number of common receptor sites including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quiscalate, kainate, glycine, alpha$_1$, alpha$_2$ or beta adrenergic, adenosine, muscarinic or nicotinic cholinergic, dopamine$_1$, dopamine$_2$, histamine$_1$, serotonin (5-HT$_1$ or 5-HT$_2$), opiate (mu, delta or kappa), sodium or calcium L and T channel sites. So what is gabapentin doing? The mechanisms of action that have been suggested are[32,33] modulation of neuronal calcium channels, agonism at GABA-B receptor subtype and modulation of neurotransmitter synthesis

Modulation of neuronal calcium channels

The key occurrence eventually leading to central sensitization is the increase in intracellular calcium concentration. Blockade of calcium channels (CaC) is therefore theoretically an attractive avenue to pursue in chronic pain therapy. However in order to be successful the variety of calcium channels has to be taken into account and selective blockade of the appropriate subtype must be the goal.

L-type CaC is the predominant form in cardiac, smooth and skeletal muscle. L stands for “lente” describing the voltage dependent slow inactivation of this channel. While blockers of the L-type CaC [dihydropyridines (nifedipine), phenylalkylamines (verapamil), and benzothiazepines (diltiazem)] have been in clinical use for a long time as antiarrhythmic, antihypertensive, and/or antianginal medication, their usefulness in treatment of chronic pain is rather limited, if existent at all.[34]

T-type CaC inactivate rapidly being open only transiently (hence T-type). A selective blocker of the T-type CaC, mibefradil, was briefly on the market before being withdrawn due to multiple drug interactions with the cytochrome P-450 3A4 enzyme.[35] Pimozide (a neuroleptic) and the succinimide antiepileptic drugs (ethosuximide and the active metabolite of methsuximide, alpha-methyl- alpha phenylsuccinimide) have T-type CaC blocking properties.[36,37] This appears also to be true for the new class of sulfonamide antiepileptics represented by zonisamide.[38] Their usefulness in treatment of chronic pain is rather limited, if existent at all.[34]

In between the slow Ls and rapid Ts there is a multitude of other CaC. The first subtype was initially found on neurons and hence designated as N-type. Subsequently P-type (from Purkinje) Q

and R (alphabetical sequence) appeared. The NPQR subgroup is resistant to blockade by the conventional calcium channel blocker.[39]

The diversity of CaC is derived from the contribution of the multitude of isoforms of the $alpha_1$, beta and gamma subunits. The main "building block" of a CaC is the $alpha_1$ subunit similar to the pore forming alpha subunit of the sodium channel (four repeat domains, each of which contains six transmembrane segments). The beta subunit is intracellular with no transmembrane domains, while the gamma subunit has four transmembrane segments. The number of subunit isoforms is increasing by the day: ten different $alpha_1$, four beta and two gamma have been identified so far. Adjacent to the CaC, there is a modulatory unit consisting of a membrane anchor (delta) and an extracellular $alpha_2$ subunit. Three delta isoforms have been identified so far.[39] While no clinically available substances are able to directly block (NPQR)-type CaC, gabapentin turns out to bind to the $alpha_2$/delta modulatory component.[40,41,42] Apparently gabapentin is able to bind to $alpha_2/delta_1$ and $alpha_2/delta_2$ but not to $alpha_2/delta_3$.[43] The net result of gabapentin binding to the modulatory unit is a reduction of calcium's ability to enter the cell.[44, 45]

Agonism at the GABA receptor

GABA receptors can be found on more than a third of all CNS neurons. They can be divided broadly into fast ionotropic (A) and slow metabotropic (B) types. The fast ionotropic GABA-A receptor is a pentameric structure assembled from a repertoire of at least 18 subunits ($alpha_{1-6}$, $beta_{1-3}$, $gamma_{1-3}$, delta, epsilon, theta, rho_{1-3}).[46] The GABA-A receptor is a "pet " target for clinicians. Indeed a multitude of widely used drugs exert their effects via this receptor. Agonists increase chloride conductance at the GABA-A controlled ionophore and thus allow chloride entrance into the cell which translates into hyperpolarization. Benzodiazepines, barbiturates, propofol, inhaled anaesthetics and alcohol act this way. In contrast, its counterpart, the slow metabotropic GABA-B receptor, has been more difficult to target: apart from baclofen which is clinically used mainly for the treatment of spasticity and hiccups, no selective substance was available.[47,48,49]

GABA-B are G-protein coupled receptors situated both pre- and postsynaptically. Stimulation of GABA-B receptors decreases calcium conductance (reduced transmitter release) and increases potassium conductance (hyperpolarization). Interestingly two GABA-B receptors form dimers described as GABA B_1/GABA B_2; this dimerization appears to be essential for the functioning of the receptor. GABA-B_1 subtypes have been identified and are designated as GABA-B_1 followed by subscripts from a to f. Gabapentin is a selective agonist at the GABA-B_1a/GABA-B_2 receptor subtype.[50,51] The relevance of this for pain therapy is not clear since the analgaesic response to gabapentin was not inhibited by a GABA-B receptor antagonist.[52]

Modulation of neurotransmitter synthesis

Following repeated treatment with gabapentin, brain GABA-transaminase (GABA-T) activity was consistently decreased and there was also a decrease in brain glutamate concentration.[53] In addition gabapentin modulates the action of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD), leading to an increased availability of GABA.[32,54,55] The relevance of these

findings for pain therapy is probably minor.

Clinical studies with gabapentin for PDN

In a double-blinded, randomized, placebo-controlled study, the efficacy of gabapentin monotherapy on pain associated with diabetic neuropathy was evaluated in 165 patients.[56] The primary efficacy measure was daily pain severity as measured on an 11-point Likert scale (0, no pain; 10, worst possible pain). By intent-to-treat analysis, gabapentin-treated patients' mean daily pain score at the study end point (baseline, 6.4; end point, 3.9; n = 82) was significantly lower compared with the placebo-treated patients' end-point score (baseline, 6.5; end point, 5.1; n = 80). Adverse effects experienced more frequently in the gabapentin group were: dizziness (24% in the gabapentin group vs. 4.9% in the control group and somnolence (23% in the gabapentin group vs. 6% in the control group). Confusion was also more frequent in the gabapentin group (8% vs. 1.2%).

In a further randomized, double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain,[57] moderate to greater pain relief was experienced in 11 (52%) of 21 patients on gabapentin and 14 (67%) of 21 patients on amitriptyline. The authors concluded that "although both drugs provide pain relief, mean pain score and global pain score data indicate no significant difference between gabapentin and amitriptyline. Gabapentin may be an alternative for treating diabetic peripheral neuropathy pain, yet does not appear to offer considerable advantage over amitriptyline and is more expensive". When used in very low doses gabapentin lacks efficacy.[58]

Hemstreet and Lapointe recently reviewed the evidence for the use of gabapentin in the treatment of diabetic peripheral neuropathy and concluded that "to date, gabapentin has been well tolerated, superior to placebo, and equivalent to amitriptyline in small clinical trials of short duration. Although overall efficacy and safety profiles appear to be favourable, larger long-term studies are needed to determine the place of gabapentin in relation to other treatment options".[59] The same task was attempted also by Laird and Gidal who arrived at virtually the same conclusion that gabapentin appears to be effective in treating various neuropathic pain disorders. Gabapentin may have advantages over current therapies, such as a favourable safety profile and lack of drug interactions; however, cost issues and limited experience may limit the use of gabapentin as a first-line option".[60] The number needed to treat (NNT) for gabapentin in PDN is quoted as being 3.7.[61] The Cochrane Database quoted NNT for effectiveness of gabapentin in PDN was 3.8 (CI 2.4 - 8.7).[62]

Adverse Drug Reaction (ADR) profile of gabapentin

Most of the reported ADR are CNS related. Among the most common ones were somnolence 20% (9% for placebo), dizziness 17% (7% for placebo), ataxia 13% (6% for placebo) and fatigue 11% (5% for placebo). Data are derived from ADR incidence in controlled trials with gabapentin as add-on drug. There is consensus that gabapentin induced ADR are minor and that the gabapentin ADR profile is benign. As with TCAs, it is important to "start low and go slow" in

increasing the dose toward the effective or maximally tolerated one.[8]

Conclusion

TCAs, by inhibiting serotonin (5-HT) and/or norepinephrine (NE) re-uptake increase the availability of the biogenic amines at the synaptic cleft and thus potentiate the inhibitory component of the nociceptive system. This translates clinically into an anti-hyperanalgesic/ analgesic effect. The efficacy of TCAs for pain relief in PDN is established. The ADR profile of TCAs, however, limits their usefulness. Gabapentin binds to the $alpha_2$/delta modulatory component of calcium channels, reducing calcium's ability to enter the cell. This translates into an anti-hyperanalgesic/analgesic effect. The efficacy of gabapentin for pain relief is comparable to that of secondary amine TCAs.

The major advantage of gabapentin over TCAs lies in the benign ADR profile. This advantage might offset the higher product price and qualifies gabapentin as an attractive alternative to TCAs.

Conflict of interest

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