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REVIEW

Arsenic exposure decreases rhythmic contractions of vascular tone through sodium transporters and K^+ channels

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Abstract

Arsenic-contaminated drinking water is a public health problem in countries such as Taiwan, Bangladesh, United States, Mexico, Argentina, and Chile. The chronic ingestion of arsenic-contaminated drinking water increases the risk for ischemic heart disease, cerebrovascular disease, and prevalence of hypertension. Although toxic arsenic effects are controversial, there is evidence that a high concentration of arsenic may induce hypertension through increase in vascular tone and resistance. Vascular tone is regulated by the rhythmic contractions of the blood vessels, generated by calcium oscillations in the cytosol of vascular smooth muscle cells. To regulate the cytosolic calcium oscillations, the membrane oscillator model involves the participation of Ca^{2+} channels, calcium-activated K^+ channels, Na^+/Ca^{2+} exchange, plasma membrane Ca^{2+}-ATPase, and the Na^+/K^+-ATPase. However, little is known about the role of K^+ uptake by sodium transporters [Na^+/K^+-ATPase or Na^+-K^+-$2Cl^-$ (NKCC1)] on the rhythmic contractions. Vascular rhythmic contractions, or vasomotion are a local mechanism to regulate vascular resistance and blood flow. Since vascular rhythmic contractions of blood vessels are involved in modulating the vascular resistance, the blood flow, and the systemic pressure, we suggest a model explaining the participation of the sodium pump and NKCC1 co-transporter in low dose arsenic exposure effects on vasomotion and vascular dysfunction.

Key words: Arsenic; Vasomotion; Na^+/K^+-ATPase; Na^+-K^+-$2Cl^-$; K^+ channels; Nitric oxide; Prostaglandin; Vascular

Core tip: Vascular tone is regulated in part by cytosolic calcium oscillations. Arsenic can induce an increase in vascular tone and resistance. We suggest a model explaining the participation of the sodium pump and Na^+-K^+-$2Cl^-$ co-transporter in low dose arsenic exposure effects on vasomotion and vascular dysfunction.

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INTRODUCTION

Arsenic toxicity is a global environmental health problem. The toxicity of this metalloid has been observed in various countries, including Taiwan[1], Bangladesh[2], Mexico[3], United States[4], Hungary[5], Argentina[6], and Chile[7]. Volcanic emission is one of the natural sources of arsenic, and individuals are majorly exposed through contaminated drinking water[8]. Smelting companies are also an important source of individual and population exposure to these kinds of heavy metals contamination. Contamination has been reported in Russia[9], United States[10], Mexico[11], Peru[12], and Chile[13]. There are few

studies showing that Chinese workers in copper smelter, steel or iron have high levels of total arsenic in urine (50 g/g creatinine). These studies include those reported for Fushun city[14], Yunnan province[15], and Fuxin city[16].

CHRONIC ARSENIC EXPOSURE AND VASCULAR DISEASES

There are epidemiologic studies that showed an association between chronic arsenic exposure and vascular diseases[17,18]. In fact, the ingestion of the arsenic-contaminated drinking water produced an increased risk for ischemic heart disease, cerebrovascular disease, and peripheral vascular resistance[19]. Other studies report positive associations between chronic arsenic exposure in drinking water, and the prevalence of hypertension[20-24].

Currently, arsenic effects on systemic blood pressure are controversial[25,26]. However, there is ample evidence that arsenic exposure mainly increases the vascular peripheral resistance[19,27], which defines the difficulty to blood flow through the blood vessels, particularly the small arteries.

Vascular rhythmic contractions, or vasomotion, are local mechanisms that regulate the vascular resistance and blood flow[28-30]. For instance, an increase in the amplitude of the rhythmic contractions cause an increased blood flow because the vascular resistance is reduced[31]. Since vascular rhythmic contractions of blood vessels are involved in modulating the vascular resistance, the blood flow, and the systemic pressure[28,29], the effects of chronic low dose exposures to arsenic on vascular rhythmic contractions becomes of great interest.

VASCULAR RHYTHMIC CONTRACTIONS

Vascular rhythmic contractions may be considered as a compensatory mechanism to preserve the perfusion of tissues[31], especially in patients with hypertension[32,33] or ischemia[34]. The mechanisms of the vascular rhythmic contractions may account for 3 states of contraction in blood vessels with different levels of calcium. These include small, medium, and tonic contraction, but only the medium concentrations produce rhythmic contractions[35]. The changes of vascular tone are generated by calcium oscillations in the cytosol of vascular smooth muscle cells[36]. To regulate the cytosolic calcium oscillations, the membrane oscillator model considers that activity of Ca^{2+} channels, calcium-activated K^+ channels, Na^+/Ca^{2+} exchange, plasma membrane Ca^{2+}-ATPase, and the Na^+/K^+-ATPase, voltage-dependent calcium channel, and transient receptor potential channel are essential for maintaining calcium oscillations[37].

ROLE OF NA^+/K^+-ATPASE AND NA^+-K^+-$2CL^-$ COTRANSPORTER ON RHYTHMIC CONTRACTIONS

Little is known about the role of K^+ uptake through Na^+/K^+-ATPase and Na^+-K^+-$2Cl^-$ (NKCC1) on the rhythmic contractions. Na^+/K^+-ATPase and NKCC1 cotransporter are responsible for the major K^+ uptake in vascular smooth muscle cells[38-40]. Recent reports demonstrates that rhythmic contractions were associated with tonic and phasic responses, the tonic dependent on $[Ca^{2+}]i$ and the phasic on potassium efflux (through K^+ channels) and potassium uptake[41,42].

Na^+/K^+-ATPase is responsible for the electrochemical gradient of sodium and potassium ions, it also plays a vital role in the regulations of ionic homeostasis in tissues and cells. In vascular smooth muscle cells, Na^+/K^+-ATPase plays a major role in the regulation of vascular tone[43,44], an increase in Na^+/K^+-ATPase activity leads to hyperpolarization and relaxation of smooth muscle[45], while its inhibition blunts rhythmic contractions in vascular smooth muscle cells[46].

It was postulated that the inhibition of K_{ATP} channels reduces extracellular K^+ and Na^+/K^+-ATPase activity, increases intracellular calcium concentration *via* Na^+/Ca^{2+} exchanger, uncouples vascular smooth muscle cells *via* gap junctions, and eliminates vascular rhythmic contractions[47,48]. Also, the inhibition of inward-rectifier K^+ channels (Kir) decrease Na^+/K^+-ATPase activity in vascular smooth muscle cells[49]. It is important to remember that the Na^+/K^+-ATPase participates in relaxation of vascular smooth muscle cells through K^+ channels. For instance, Na^+/K^+-ATPase is involved in K^+-induced vasodilatation of hamster cremasteric arterioles[50], and vasodilation in the human forearm[51]. When K^+ (1 to 15 mmol/L) accumulates in the extracellular space, Na^+/K^+-ATPase activity increases efflux of potassium through Kir. This leads to hyperpolarization and vasodilatation of the vascular smooth muscle cells[49,52]. In contrast, the opening of calcium-activated K^+ channels inhibits the Na^+/K^+-ATPase function[53,54], and vascular rhythmic contractions[28].

NKCC1 is an obligatory symport system with an apparent stoichiometry of 1:1:2 sodium, potassium and chloride ratios respectively. Although the co-transporter is bidirectional in resting vascular smooth muscle cells, the sum of the electrochemical gradients for the three transported ion species determines net influx[55].

Evidence for the role of NKCC1 co-transporter on vascular rhythmic contractions is scanty, but it is worthy of note that the inward current of Cl^- decreases rhythmic contractions by increasing vasoconstriction[47]. NKCC1 is responsible in part to keep intracellular Cl^- concentration above the electrochemical equilibrium[56] as such helping to maintain the electrochemical gradient and cellular reactivity. Phenylephrine-induced stimulation of NKCC1 increases intracellular Cl^- concentration, depolarize vascular smooth muscle cells[57], open L-type calcium channels[58] and produce vasoconstriction. In the vascular oscillator model[59], the release of intracellular Ca^{2+} from the reticulum stimulates the inward current of Cl^- *via* the calcium-activated Cl^- channel[60] and cyclic guanosine monophosphate (cGMP)-activated Ca^{2+}-dependent Cl^- channels[61]. This leads to membrane depolarization, opening

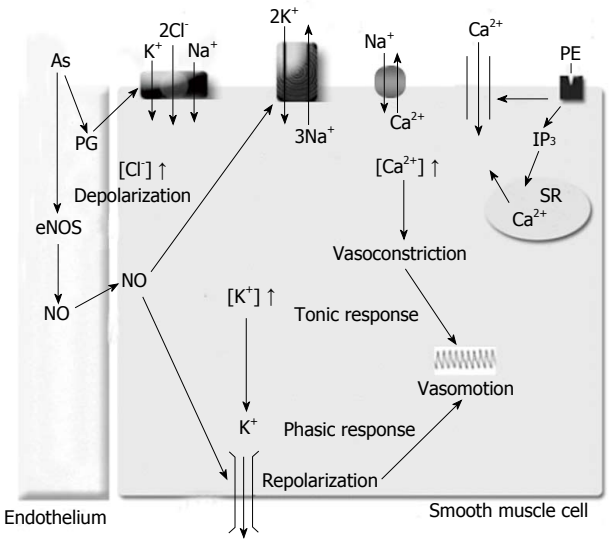

Figure 1 Putative model of arsenic effect on vasomotion phenomenon in blood vessels. The figure shows the stimulation of the Na^+/K^+-ATPase by endothelial nitric oxide (NO) and stimulation of the Na^+-K^+-$2Cl^-$ cotransporter by endothelial prostaglandins (PG). Arsenic would reduce NO bioavailability or would increase PG level, both of them would produce an increase in vasoconstriction or a decrease in the repolarization of the cell membrane, respectively, and then would reduce vasomotion. PE: Phenylephrine; As: Arsenic; eNOS: Endothelial nitric oxide synthase; SR: Sarcoplasmic reticulum.

L-type calcium channels and reduction in the oscillations of vascular tone. Therefore these findings suggest that the cotransporter NKCC1 would be responsible, in part, for vasoconstriction by chloride.

EFFECT OF ARSENIC ON VASCULAR RHYTHMIC CONTRACTIONS

Vascular rhythmic contractions are dependent in part on endothelial nitric oxide (NO)[46], but there are few studies showing that the arsenic reduces vasomotion (vascular rhythmic contractions) by decreasing the NO bioavailability[62].

It is well established that heavy metals such as arsenic induce increases in vascular resistance by inducing vascular endothelial dysfunction (VED)[62,63]. VED consists of a reduction in endothelium-dependent vasorelaxation caused by a decrease in the release of endothelial NO[64]. Arsenic-induced VED is caused in part by oxidative stress.

Oxidative stress from pollutants like arsenic causes an increase in the reactive oxygen species, this leads to a modification of amino acids of proteins, mainly sulfur-containing amino acids methionine and cysteine[65]. Arsenic causes oxidative stress through peroxynitrite generation in aortic endothelial cells, producing loss of biological activity in enzymes and proteins[66,67]. In this context we had shown that chronic arsenic exposure in drinking water reduced acetylcholine-induced relaxation in female rat aorta[68], impairment of the endothelial nitric oxide synthase activity and decreasing of endothelial NO production[69,70].

NO is reported to activates Na^+/K^+-ATPase function[71], we observed that acetylcholine and sodium nitroprusside (SNP) induces activation of Na^+/K^+-ATPase activity, and SNP effect is abolished by inhibition of PKG (KT-5823)[72]. Cogolludo *et al*[73] (2001) showed that SNP activates Na^+/K^+-ATPase in mesenteric piglet's arteries while Tamaoki *et al*[74] (1997) found that cGMP activates Na^+/K^+-ATPase in pulmonary artery smooth muscle cells.

Since arsenic decreases the NO bioavailability[62], and the NO increases Na^+/K^+-ATPase function[71] which enhances the vascular rhythmic contractions, we may suggest that arsenic decreases the vascular rhythmic contractions by Na^+/K^+-ATPase function (Figure 1). Similar conclusions would be expected with the Kir channel, as Chen *et al*[75] (2010) demonstrated that arsenic trioxide produces down-regulation of Kir channel in cardiomyocytes of rats, and the Kir channel function increases Na^+/K^+-ATPase activity[49].

Although the endothelial NO does not affect NKCC1 co-transporter function[76], the endothelial prostaglandins increase NKCC1 activity thereby enhancing the contractile response to agonist in rat aorta[77-80]. Moreover, the endothelial prostaglandins increase agonist-induced rhythmic contractions in rat aorta[81], rat mesenteric artery[82], and arterioles of the cheek pouch of male hamsters[42]. Furthermore, arsenic increases the cyclooxygenase-2 (COX-2) protein in aortic endothelial cells[67], COX-2 in HUVEC[83], and enhances COX-1 and COX-2 activities in hind paw muscle of male rats[84]. Therefore, as a result of the prostaglandins effect on the vascular contractility through NKCC1 described above, arsenic might increase the vascular rhythmic contractions by NKCC1 co-transporter function.

The major toxic species of arsenic used in several studies are arsenite (trivalent inorganic arsenic, *i.e.,* arsenic trioxide) or arsenate (pentavalent inorganic arsenic). Although the concentration of arsenate in drinking water is higher than those of arsenite, toxic effects of arsenate have not been properly documented. Arsenate is mainly metabolized by organisms as monomethylarsonic acid and dimethylarsinic acid, which significantly are not toxic[85]. However, this theory of the methylation of inorganic arsenic as a detoxification process has been revised[86] as other trivalent methylated species with higher toxicity have been reported[87]. Possibly, the biological effect of arsenate is mainly by reduction to arsenite[88].

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MINIREVIEWS

Pharmacological management of neuropathic pain in patients with vestibular schwannomas: Experience of the Atlantic Lateral Skull Base Clinic

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Abstract

Neuropathic pain is chronic pain generated by disorders of the peripheral and central nervous system, including skull base tumours. A skull base tumour can be any type of tumour that forms in the skull base, and this includes vestibular schwannomas which arise from the sheath of the inner ear vestibulocochlear nerve (eighth cranial nerve). Growth of the tumour, surgical resection, and/or stereotactic radiotherapy may result in compression and/or irritation of the fifth cranial nerve (trigeminal nerve) resulting in facial pain and/or numbness. Non-trigeminal afferent input may contribute to the wide constellation of symptoms seen in orofacial pain patients. The purpose of this report was to develop a decision tool to guide the recognition and treatment of neuropathic pain in this specialized population. Recommendations for treatment are based on evidence presented in Canadian and international neuropathic treatment guidelines. Algorithms are included for assessment and treatment of adult patients with agents that are recognized to have analgesic efficacy within the broad context of neuropathic pain.

Key words: Acoustic neuroma; Stereotactic radiotherapy; Tricyclic antidepressants; Serotonin-norepinephrine reuptake inhibitors; Calcium channel modulators; Tramadol; Opioids

Core tip: The complexity of managing trigeminal neuralgia and neuropathic pain conditions among patients with skull base tumors requires a simple albeit comprehensive treatment algorithm that can be employed effectively by general practitioners, surgeons and other primary care prescribers in acute care or ambulatory clinical settings. We describe a simple treatment algorithm formulated on recommended best practice and based on clinical experience. It is intended to guide treatment, facilitate management and evaluation of outcome data (self-reported pain, quality of life measures) to elucidate the use of standardized approaches to pain management in patients with skull base etiology.

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INTRODUCTION

This report considers pharmacological approaches to be used within the skull base tumour health community. Its intent is to offer assistance in treating patients who present with neuropathic pain (NP) in the context of orofacial, head and neck pain, including trigeminal neuralgia (TN), which is the most common craniofacial pain syndrome that is neuropathic in origin. The impetus for assembling the information stems from the experiences of practitioners within an interdisciplinary clinic who consistently rely on formularies and consultation with colleagues for advice in treating neuralgia and NP. The document offers suggested algorithms for assessment and treatment of patients with agents that are recognized to have analgesic efficacy within the broader context of NP. It makes the distinction between generalized NP[1] and NP due to skull base tumours affecting the head, neck, face and glossopharyngeal region[2,3], but also recognizes commonalities in mechanisms underlying various forms of NP[1].

The Atlantic Lateral Skull Base Clinic

Vestibular schwannomas (VS) are slow growing, benign neoplasms that may be life threatening due to compression of central structures. Extra-axial tumours arising from the Schwann cell sheath of the vestibular or cochlear nerve (8th cranial nerve) are referred to as acoustic neuromas or, more appropriately, VS. Clinical diagnosis of a VS suggests an incidence of 0.7-1 per 100000 people, although incidental (*i.e.*, non-clinically relevant) discovery of VS suggests an incidence as high as 2 per 10000 people[4]. In some cases, VS are associated with NP and TN, often secondary to tumour compression or stereotactic radiation treatment affecting cranial nerves within the cerebellopontine angle (CPA).

The Atlantic Lateral Skull Base Clinic provides coordinated care through Neurootology (Division of Otolaryngology), Neurosurgery and the Stereotactic Radiotherapy Group to patients with unilateral or bilateral VS, other CPA tumours, as well as lesions of the petrous apex and jugular foramen. This program is unique in Canada, offering a single centre, multidisciplinary approach for lateral skull base lesions. The Atlantic Lateral Skull Base Clinic serves a population of more than 2 million people in a catchment area that includes Newfoundland, Prince Edward Island, New Brunswick and Nova Scotia[5]. Treatment options for skull base tumours include monitoring clinical progression, surgery, stereotactic radiation therapy (SRT), balance and hearing rehabilitation. An interdisciplinary clinic provides an ideal environment in which to identify and intervene in the treatment and management of NP affecting the head and neck region. The focus of this work is on clinical experiences within our clinic. With low incidence, it will be very unlikely there will ever be randomized clinical trials that provide direct guidance for pain management in patients with VS. In that event, one must rely on extrapolation, and what we report is implementation of that approach and what it looks like in clinic.

Disease background

NP is a chronic pain state that is initiated by peripheral and central nervous system injury caused by trauma, inflammation, infection or metabolic disease, and includes conditions such as distal polyneuropathy due to diabetes (diabetic neuropathy, or DN) and post-herpetic neuralgia (PHN)[1]. The Canadian Pain Society (CPS) estimates (based on 8.2% chronic NP prevalence in the general population) that 1 million Canadians live with NP[6-8]. Neuropathic pain interferes with activities of daily living and work performance, impairs mood, decreases quality of living and generates three-fold increases in health care costs relative to matched controls[9]. NP conditions involve spontaneous (paroxysmal or ongoing) and stimulus-evoked (*e.g.*, mechanical and thermal) symptoms; continuous or intermittent spontaneous pain is frequently described as burning, stabbing, shooting or shock-like; stimulus-evoked pain includes allodynia (pain in response to non-painful stimulation, extreme sensitivity to touch) and hyperalgesia (enhanced response to painful stimuli); NP can also involve tingling and numbness[1,6,9].

TN involves irritation or compression of the 5th cranial nerve (trigeminal nerve), which evokes paroxysmal episodic stabbing pain of the facial area. Classically, pain is described as a sharp, shooting, electric shock-like, unilateral pain with acute onset and termination in distribution of the trigeminal nerve; this usually involves the V2 (maxillary) and V3 (mandibular) divisions but is rare in the V1 (ocular) division[10]. TN has an incidence of 4-28 per 100000 person years[11,12]. It can arise due to vascular alterations, non-vascular lesions, or tumours and other skull base abnormalities which exert pressure on the trigeminal nerve located in the CPA. Trigeminal NP is more continuous, and is characterized as burning, aching, throbbing[10]. VS, or acoustic neuromas, are the most frequent CPA tumour to cause TN-like symptoms[13]. Non-trigeminal nociceptive input, concurrent with induced masticatory responses (*i.e.*, hypoglossal, spinal accessory, facial, glossopharyngeal and vagal motor centers), may contribute to the wide constellation of symptoms seen in orofacial pain patients[14]. The distinction between TN and trigeminal NP is important, as there are different treatment recommendations for each[1,10].

Current algorithms

Treatment guidelines and decision rules improve patient outcomes. Recent literature providing strategies for the treatment of NP include the consensus statement and guidelines from the CPS[6], as well as the Neuropathic Pain Special Interest Group of the International Associa-

tion for the Study of Pain[15,16]. It needs to be emphasized that most recommendations have been derived from studies on PHN and diabetic neuropathy (DN). The European Federation of Neurological Societies (EFNS) Task Force included an approach to the management of NP pain associated with damage to the trigeminal nerve[17].

There remains a paucity of information on how to assess, diagnose and treat pain in patients with VS or other skull base tumours, pain that appears to be of neuropathic origin and typically resides within the head, face, neck and glossopharyngeal area. In order to provide guidance relating to this specialized patient population, we constructed an algorithm for NP and craniofacial pain, including TN, based on Canadian contemporary standards of care and existing NP treatment algorithms. Recommendations consider pharmaceutical agents with evidence of efficacy in neuropathic pain, patient tolerability of the dose range expected to be needed, and actual therapeutic efficacy observed within our clinical practice. To date, there has not been a published tool that provides a clearly-defined algorithm for the assessment and treatment of NP in patients with skull base tumours. It is intended that this report provides guidance to primary care practitioners treating NP in patients with skull base tumours, using specific drugs or combinations of drugs, to improve outcomes in clinical practice with respect to patient self-reports of pain and quality of life.

CHARACTERIZATION OF PAIN ASSOCIATED WITH SKULL BASE TUMOURS

Skull base tumours involve the proliferation of abnormal cells in the part of the brain that meets the base of the skull. Symptoms of skull base tumours may include twitching, paralysis or facial pain. Craniofacial NP disorders include neuropathies, neuromas and neuralgias. Although significant interpractitioner and institutional variability exists, facial neuropathy and trigeminal nerve disturbances are relatively uncommon in comparison with unilateral hearing loss, tinnitus and vertigo or even idiopathic headache[18,19]. Even if uncommon, when a patient presents with what appears to be NP, the origin of the pain and appropriate treatment actions may be more difficult to determine than the existence of pain. At the very least, the challenge is to identify where the pain is coming from and to distinguish it from idiopathic headaches. Headaches are present in 50%-60% of patients with unilateral VS at the time of diagnosis[4,20]. Clinically, headaches that are unresponsive to over-the-counter analgesics may be a subtle cue that the pain originates from compression of the cranial nerves by the tumour[21]. It has been reported that 3% to 45% of patients with CPA VS experience facial paresis, facial neuropathy and trigeminal nerve disturbances (hypoesthesia, paresthesia, and neuralgia) due to compression by the tumour on the ipsilateral[13,22], and less commonly, on contralateral[23] cranial nerves; up to 93% are at risk secondary to irradiation treatment[24-27].

The incidence of pain following SRT treatment is common. It has been estimated that 93% of lesions treated with SRT leave the patient at risk of radiation-induced TN[26]. Other centers report that trigeminal symptoms occur in $\geqslant$ 3% of patients whose tumours approach the level of the trigeminal nerve[25]. It is also important to distinguish NP from pain associated with hydrocephalus which may occur following tumour irradiation[19]. As such, patients presenting with pain should be referred for a magnetic resonance imaging (MRI) or computerized tomography scan. It is evident, given the diversity of pain mechanisms and individual patient responses that no single drug works for all NP states. In this respect, successful management of pain syndromes first necessitates accurate assessment.

PHARMACOLOGICAL MANAGEMENT OF NEUROPATHIC PAIN

Assessment of pain and associated symptoms is necessary for diagnosis and management of NP. The self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs scale and the French Neuropathic Pain Group clinician-administered questionnaire called DN4 may be used, based on their high sensitivity and selectivity[1,28,29]. The use of these tools is meant to complement but not replace clinical judgment.

Current treatment guidelines provide an evidence-based approach to the treatment of NP. Treatment guidelines have been developed based on data collected from randomized controlled clinical trials of anticonvulsants (carbamazepine, oxcarbazepine), tricyclic antidepressants (TCAs) (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine), calcium channel ligands (gabapentin, pregabalin), local anesthetics (5% lidocaine patch), opioids (morphine, methadone) and opioid-like hybrid drugs (tramadol)[6,16,17]. It should be mentioned that if the 5% lidocaine patch is unavailable, a lidocaine gel formulation or compounded cream may be substituted, although limited efficacy in non-post-herpetic pain has been reported[30]. A general overview of our suggested algorithm for the management of NP in our clinic is presented in Figures 1 and 2.

The algorithms presented below are based on published clinical guidelines to simplify the management and evaluation of NP in patients with lateral skull base tumours. Suggested first, second and third line agents [determined by efficacy, indicated by number-needed-to-treat (NNT), and patient tolerability as indicated by number-needed-to-harm (NNH), or side-effects] are listed in Figure 3. NNT and NNH vary according to the etiology of the pain and reference consulted[31,32]. Algorithms for individual pharmacological agents include initial starting doses, titration doses, temporal intervals and maximal dosing schedules[33]. In addition, TCAs, SNRIs, gabapen-

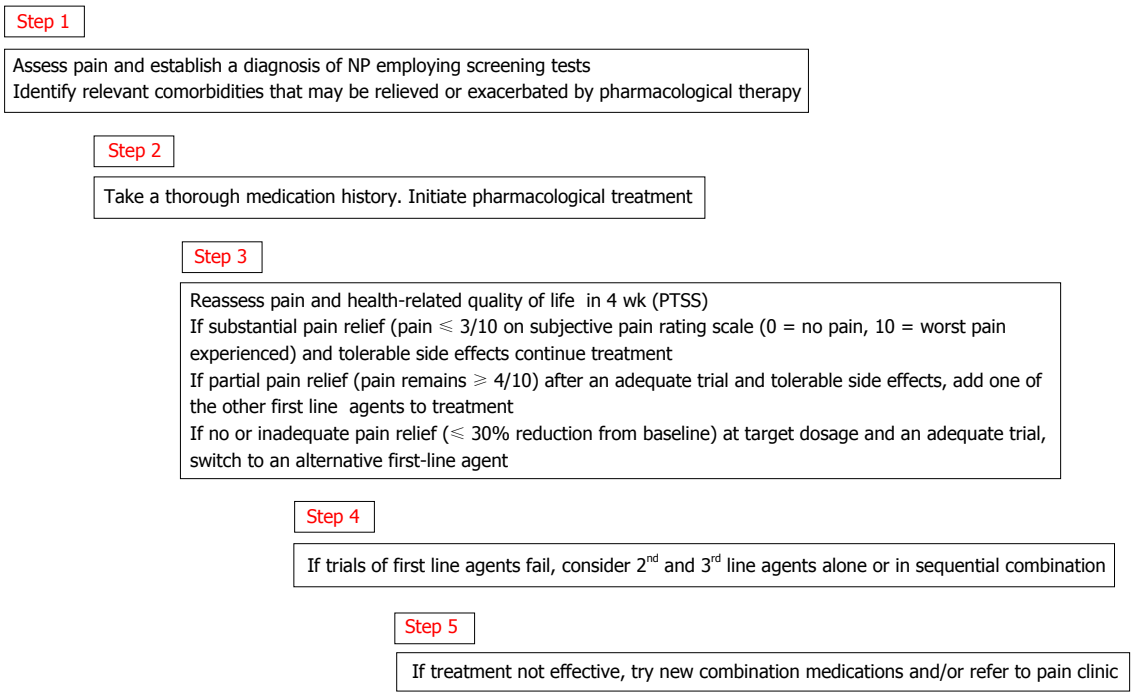

Figure 1 Assessment and management of neuropathic pain. NP: Neuropathic pain; PTSS: Pain treatment satisfaction scale.

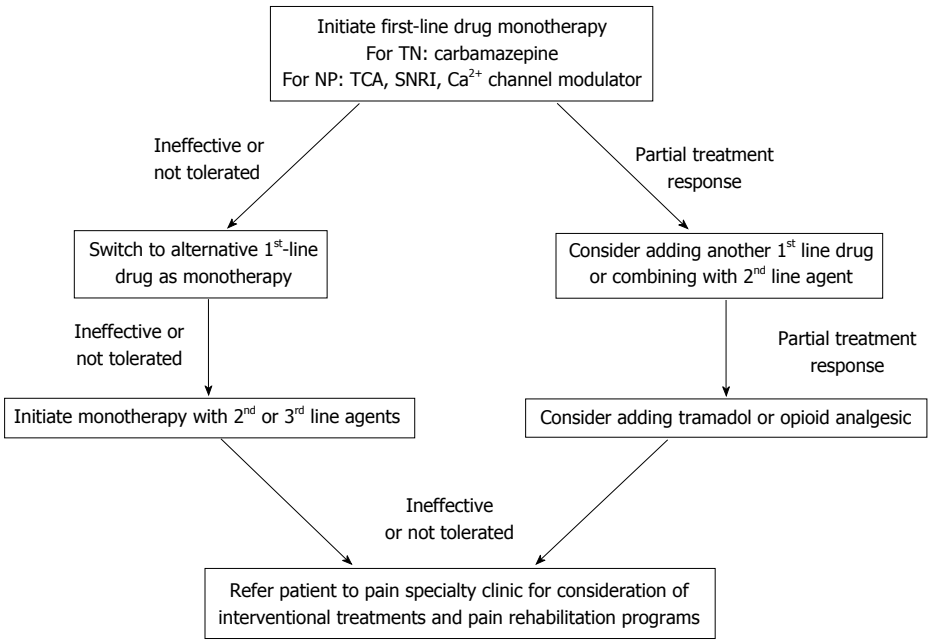

Figure 2 Management of neuropathic pain or trigeminal neuralgia in the Atlantic Lateral Skull Base Clinic. NP: Neuropathic pain; TN: Trigeminal neuralgia; SNRI: Serotonin-norepinephrine reuptake inhibitor.

tinoids, opioid analgesics and tramadol must all be used with caution in elderly patients because of the risk of falls and cognitive impairment[15,16]. Recommendations are also made regarding the duration of adequate trials at maximum tolerated dosages to evaluate the impact on self-reported pain.

Initial and subsequent agents

For management of classical TN (characterized by paroxysmal, unilateral pain), carbamazepine is the first choice, but otherwise it is not used; this agent has a NNT around 1.9 with virtually complete pain relief[6,10,34-36] (Table 1). Oxcarbazepine can, and should, be substituted for carbamazepine if there is an unacceptable side effect profile[10,34-36] (Table 1).

For management of NP, there are several TCAs available, but amitriptyline and nortriptyline are commonly used, and exhibit NNT values of 1.3-3.6[32,37-39]; NNH values are 3-6 for minor, and 14-28 for major, harm. The analgesic properties of TCAs are independent of their an-

Table 1 Summary of drugs used for management of trigeminal neuralgia and neuropathic pain

Drug	Action	Dosing	Common side effects[1]
CBZ	Blocks Na^+ and Ca^{2+} channels	300-1000 mg; 100 mg BID initially, increase by 200 mg weekly Adequate trial 8-12 wk, 2 wk at maximal dose	Drowsiness, ataxia, headaches, nausea, vomiting, constipation, blurred vision, rash Drug interactions Taper doses when discontinuing
OXC	Keto derivative of CBZ, same actions	Equivalent efficacy to CBZ; 300-2400 mg; 300 mg BID initially, increase by 600 mg weekly Adequate trial 8-12 wk, 2 wk at maximal dose	Improved tolerability compared to CBZ Vertigo, fatigue, dizziness, nausea, hyponatraemia in high doses No major drug interactions Taper doses when discontinuing
TCAs or tricyclic antidepressants: nortriptyline, amitriptyline	Block NA and 5-HT reuptake, block Na^+ channels, interact with several neurotransmitter systems	Nortriptyline 10 mg (elderly) or 25 mg (adult) at bedtime; increase dose by 10 or 25 mg every 3-7 d; up to 75-100 mg daily Adequate trial 6-8 wk, 2 wk at maximal dose Amitriptyline doses similar	Nortriptyline is better tolerated than amitriptyline Dry mouth, constipation, blurred vision, sedation, orthostatic hypotension Taper doses when discontinuing
SNRIs or serotonin-noradrenaline reuptake inhibitors: Duloxetine, Venlafaxine	Similar actions to TCAs, but fewer interactions with receptor systems	Duloxetine: 60 mg/d, increase to 120 mg after 1 wk Venlafaxine: 75 mg/d, increase to 225 mg over 3 wk Adequate trial 4-6 wk, 2 wk at maximum dose	Headache, nausea, dry mouth, sleepiness, fatigue, constipation, dizziness, decreased appetite, and increased sweating. Taper doses when discontinuing Drowsiness, dizziness, weakness, feeling nervous, tinnitus, increased sweating, blurred vision, dry mouth, changes in appetite or weight, facial flushing, mild nausea, constipation, sexual side-effects Taper doses over 7-10 d when discontinuing
Gabapentin	Ca^{2+} channel modulator	100-300 mg TID, increase dose every 1-7 d; maximum dose 3600 mg daily Adequate trial 3-8 wk titration, 2-8 wk at maximal dose	Dizziness, sedation, weight gain, weakness, tiredness, nausea, diarrhea, constipation, blurred vision, headache, breast swelling, dry mouth, fatigue, myalgia, loss of balance or coordination Taper doses when discontinuing
Pregabalin	Ca^{2+} channel modulator	50 mg OD or 25 mg BID, double dose each week; maximum daily dose 600 mg Adequate trial is 4 wk at maximal dose	Dizziness, drowsiness, loss of balance or coordination, problems with memory or concentration, anxiety, depersonalization, hypertonia, hypesthesia, decreased libido, nystagmus, paresthesia, twitching, breast swelling, tremors, dry mouth, constipation Taper doses when discontinuing (minimum of one week)
Tramadol	Inhibits NA and 5-HT reuptake, binds opioid receptors	50 mg BID, increase by 50-100 mg daily in divided doses over 3-7 d as tolerated; 400 mg is maximum dose (300 mg in elderly) Adequate trial is 4 wk at maximum dose	Dizziness, spinning sensation, constipation, upset stomach, headache, drowsiness, feeling nervous or anxious
Morphine	Interacts with mu opioid receptors in spinal cord and brain, regulates synaptic activity in pain pathways	10-15 mg q4h or prn (equianalgesic doses for other opioids); after 1-2 wk, convert to long-acting opioid (*e.g.*, CR hydromorphone) Titration allows for dose escalation Adequate trial is 4-6 wk	Sedation, pruritus, constipation, diarrhea, weight loss, nausea, vomiting, stomach pain, loss of appetite, flushing (warmth, redness, tingling), headache, dizziness, spinning sensation, memory problems, sleep problems (insomnia), strange dreams Taper doses when discontinuing

[1]These are not a complete list of side effects and others may occur. CBZ: Carbamazepine; 5-HT: Serotonin; NA: Noradrenaline; OXC: Oxcarbazepine; q4h: Every four hours; BID: Twice a day; TCA: Tricyclic antidepressant; SNRI: Serotonin-norepinephrine reuptake inhibitors; prn: Pro re nata; TID: Three times a day; OD: Once daily; CR: Continuous release.

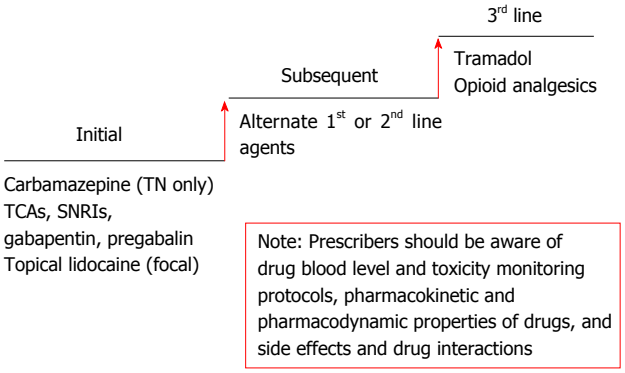

Figure 3 Treatment algorithm for trigeminal neuralgia or neuropathic craniofacial pain. TN: Trigeminal neuralgia; SNRIs: Serotonin-norepinephrine reuptake inhibitors; TCA: Tricyclic antidepressant.

tidepressant effects, and several mechanisms, in addition to blockage of serotonin and norepinephrine reuptake, are involved in their actions[40]. It should be emphasized that caution must be employed with the use of TCAs in older patients because of anticholinergic adverse effects, sedation, risk of falls, and risk of cardiac toxicity. Nortriptyline, a metabolite of amitriptyline with similar pharmacological effectiveness reflected in similar NNT values[6,37,39], has a lower incidence of adverse effects compared to amitriptyline[32,41]. The lowest effective dose of TCA should be used in NP patients, avoiding patients with ischemic heart disease or increased risk of cardiac death[15] (Table 1). Where available, lidocaine medicated plaster (NNT = 4.4, NNH = 29), a topical formulation, can be considered first-line treatment if the pain is focal

and there are tolerability issues for oral formulations[16,37].

The EFNS and Neuropathic Pain Special Interest Group (NeuPSIG) recommend the two SNRIs, duloxetine and venlafaxine, as first-line options, while Canadian guidelines consider these second-line options for treatment of NP. Duloxetine (NNT = 5-6; NNH = 7-9 minor, 13-15 major) has primarily been examined in DN, while venlafaxine (NNT = 3-5, NNH = 7-9 minor, 16 major) has been examined in a broader range of NP conditions[31,37-39] (Table 1). Venlafaxine may be employed in combination with gabapentin to increase its efficacy[16,30,42,43].

The Consensus Statement and Guidelines from the Canadian Pain Society list gabapentin and pregabalin as first-line agents in the treatment of NP[6]. Most of the literature and guidelines for NP are based on PHN and DN and may not be applicable to all NP conditions[9,15]. Gabapentin (NNT = 4.1-6.4, NNH = 3.7) and pregabalin (NNT = 3.3-6.0, NNH = 3.7-8.8) (Table 1)[32,37,38] can be considered as first- or second-line agents for management of orofacial NP associated with skull base tumours. The EFNS Task Force has identified the usefulness of combination therapy, including TCA-gabapentin for the management of NP and TN[17] (Figure 2).

Gabapentin and pregabalin decrease the release of several neurotransmitters involved in pain through binding to the α2-δ subunit of voltage-gated calcium channels, synaptic γ-aminobutyric acid modulation and synaptogenesis[44]. Side effects of gabapentin include dry mouth, dizziness, gastrointestinal disturbances and cognitive impairment. There is some evidence that the efficacy of gabapentin is increased in painful DN, when combined with venlafaxine or morphine[31,45]. Combination of gabapentin with nortriptyline was superior to either drug alone, and combination of gabapentin with opioids has shown increased efficacy for the treatment of TN and NP[17] (Figure 2).

Third-line agents

Tramadol, a hybrid drug with SNRI and μ-opioid agonist properties, has a NNT = 3.4-4.9, and a NNH = 7.7; it should not be combined with TCAs due to increased risk of serotonin syndrome[32,37] (Table 1). Opioids are generally safe if titrated slowly[46]. While there is some evidence to support opioids in NP[15,32,37,39], opioids as primary therapy are not always effective, and combination therapy may be needed[31,42,44]. The analgesic efficacy of a combination of morphine and gabapentin was increased compared to each individual agent in patients with PHN and painful DN; however, while the maximal tolerated doses were lower in combination therapy, there was report of increased adverse effects[16].

There are many liabilities and controversies surrounding the use of opioids in those with chronic non-cancer pain[28,46]. For treating NP with opioids we follow recommendations of the 2010 National Opioid Use Guideline Group[46]; referral to a chronic pain service is indicated when combination therapies involve primary and adjuvant treatment beyond the common agents listed.

Other agents

Although beyond the scope of this document and better reserved for pain specialty clinics, interventional procedures, compounded drugs (such as carbamazepine, gabapentin, antidepressants, lidocaine) delivered as topical formulations for the orofacial region[47], invasive techniques (may include intravenous lidocaine)[6] or intradermal botulinum toxin[16] may be considered. Several recent case series reports and a controlled study support the efficacy and safety of botulinum toxin for TN[48-50]. Future treatment guidelines will position these options within current schemes.

CASE EXAMPLES

Two case examples of the presentation and treatment of neuropathic pain resulting from VS are outlined below.

Case 1

Presentation and diagnosis: RG, a 72-year-old retired fireman, presented to the Atlantic Lateral Skull Base Clinic in August 2010 with progressive right-sided hearing loss and tinnitus over 1-2 years with a new presentation of numbness and tingling on the right side of his face including the tip of his tongue. MRI revealed a right-sided cerebellar pontine angle tumour (25 mm × 27 mm) in the axial plane with mass effect on the brainstem consistent with a vestibular schwannoma/acoustic neuroma. RG opted for stereotactic radiation therapy (SRT) over surgery or a more conservative "wait and scan" approach.

Symptoms prior to treatment: In December 2010, prior to SRT therapy, lidocaine hydrochloride swish and spit was ineffective in controlling symptoms. In January 2011, he reported exacerbation of symptoms on the right side of his face, dysesthesia rather than numbness, constant burning involving the tip of the tongue and the bottom of the tongue on the right hand side; symptoms were exacerbated by eating. He had lost 30 pounds due to decreased food intake. Pregabalin 75 mg twice a day and dexamethasone 4 mg every morning with breakfast was prescribed. Over the next month, pregabalin was increased to 150 mg twice a day as he noted some early improvement. The pregabalin dose was again increased to 300 mg and RG gained 3 pounds.

Treatment and follow up: SRT began in February 2011. RG noticed an immediate improvement in his tinnitus. In March 2011, gabapentin replaced pregabalin and was increased to 1800 mg/d while dexamethasone weaning began. RG experienced hypotension in response to the increase in gabapentin and the dose was decreased to 300 mg three times a day. SRT was completed in April 2011. At this time, RG reported increased facial pain, so gabapentin was increased to 1200 and then 1500 mg/d. RG was not reporting any relief from symptoms, and numbness and right-sided trigeminal neuralgia persisted. In October 2011, he was weaned off gabapentin, and amitriptyline was prescribed for facial pain 10 mg every night, and increased to 20 mg after 1 wk. In November

2011, he reported side effects which included sleepiness and nausea. His family doctor changed the prescription to nortriptyline 10 mg for 5 d, then 20 mg/d for 5 d, and then 30 mg/d, with a plan to increase this again in the next 5 d to 50 mg/d, his current dose in February 2012. He has improved facial pain and reports improvements in eating and tasting food. He still has some paresthesia and dysesthesia in the right side of his face in the trigeminal distribution in all 3 branches. His vestibular schwannoma has shrunk by 0.5 cm.

Case 2

Presentation and diagnosis: DB aged 71, presented to the Atlantic Lateral Skull Base Clinic in March 2008 reporting a recent history of loud noises prompting headaches. She subsequently had an audiogram which showed slight decrease in useful hearing on the right side compared to the left. An MRI (November 2007) revealed a small right-sided acoustic neuroma (18 mm × 9 mm in the axial plane). General ears, nose and throat exam was normal, other than the slight decrease in useful hearing; no tinnitus or vertigo was reported. The Unterberger stepping test revealed a moderate pulling to the right; cerebellar and oculomotor function was normal. Her facial nerve was completely normal with no facial weakness, facial twitching or facial numbness. She remained stable for a year.

Symptoms prior to treatment: In July 2009, her hearing deteriorated, to 60% of normal, and she was experiencing disequilibrium. MRI revealed slight growth in the neuroma (20 mm in longest dimension, 13 mm perpendicular to the petrous apex). A subsequent MRI in November 2009 showed further growth (20 mm × 15 mm).

Treatment and follow up: DB was referred for SRT, and this was completed June 2010. MRI in January 2011 revealed central cystic changes in tumour composition consistent with SRT. DB reported no new clinical symptoms other than further decrease in hearing on the right side.

In March 2011, new neurological symptoms emerged. Initially she described the right side of her tongue as heavy. She began to have some right-sided painful secondary paresthesia on her face in cheek area, upper and lower lips and tongue [maxillary (V2) and mandibular (V3) divisions of the trigeminal nerve] that she describes as a persistent burning sensation that is made worse by eating. She also described discomfort in her right eye and right-sided facial twitching. MRI in March 2011 showed swelling of the tumour in the right CPA consistent with SRT-induced changes. She was started on gabapentin 300 mg once daily for one week, increasing the dose to twice daily the second week, and thrice daily for the third week if tolerated.

In November of 2011 she returned. Gabapentin 300 mg once daily reduced her symptoms; however, it was associated with intolerable constipation and myalgia in the upper arms. She was weaned off gabapentin and her constipation and myalgia dissipated. The right-sided acoustic neuroma had further decreased in size, approximately 18 mm × 12 mm (May 2013) compared to 22 mm × 16 mm (April 2012), yet she continued to experience persistent chronic orofacial pain. While it is possible that DB would be refractory to other pharmacologic interventions, she has declined further interventions, despite the pain and effect on her quality of life.

CONCLUSION

The present report describes evidence for application of pain management strategies in patients with VS. A decision tool and treatment algorithm is presented to facilitate evaluation and management of patients with NP resulting from skull base disorders. A pharmacological algorithm, with primary and adjuvant treatment, summarizes pharmaceutical choice and management of NP and TN in patients with VS and can be made available in the clinic for quick review by the treating physicians. This instrument is intended to guide treatment of neuropathic/trigeminal pain in patients in acute care or ambulatory clinical settings. Essential to the comprehensive management of patients is evaluation of the effects of the intervention on quality-of-life and patient satisfaction with pain management. Patient satisfaction with pain management, using the Pain Treatment Satisfaction Scale[51], as well as the American Pain Society Satisfaction Survey, was influenced by effectiveness of medication on pain severity, independent of initial pain intensity, and by communication[52]. Comparison of outcome data (self-reported pain and quality of life) will elucidate the use of standardized approaches to managing pain among patients with specific skull base etiology. The purpose of the present treatment algorithm was to develop a common scheme that may be utilized by beginning practitioners for treating this relatively uncommon, but clinically challenging, condition.

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Acknowledgments

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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