Review Article

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Narrative review: the evidence for neurotoxicity of dental local anesthetics

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Dental local anesthesia is performed daily on a global scale. Adverse effects are rare, but the topic of neurotoxicity of local anesthetics deserves to be explored, as publications can be controversial and confusing. Therefore, a need was felt to address and question the evidence for potential neurotoxicity of dental local anesthetics. This review aimed to assess the studies published on the neurotoxicity of dental local anesthetics. A Pubmed® search was conducted between January 2019 and August 2019. This revealed 2802 hits on the topic of neurotoxicity or cytotoxicity of the following anesthetics: lidocaine, prilocaine, mepivacaine, articaine, ropivacaine, and bupivacaine. Only 23 papers were deemed eligible for this review: 17 *in vitro* studies, 3 reviews and 3 audits of national inquiries. The heterogeneous literature on this topic showed that all dental local anesthetics are potentially neurotoxic in a concentration and/or exposure time fashion. There seems no consensus about what cell lines are to be used to investigate the neurotoxicity of local anesthetics, which makes the comparison between studies difficult and ambiguous. However, the bottom line is that all dental local anesthetics have a neurotoxic potential, but that there is no unanimity in the publications about which local anesthetic is the least or the most neurotoxic.

Keywords: Local Anesthetics; Neurotoxicity.

INTRODUCTION

The definition of neurotoxicity, according to the National Institute of Neurological Disorders and Stroke [https://www.ninds.nih.gov/Disorders/All-Disorders/Neurotoxicity-Information-Page#disorders-r1], is an altered normal activity of the nervous system after its being exposed to natural or man-made toxic substances (neurotoxins). Neurotoxins can eventually disrupt or even kill neurons, key cells that transmit and process signals in the brain and other parts of the nervous system. Neurotoxins can potentially come from substances used in chemotherapy, radiation treatment, drug therapies, and organ transplants, but also heavy metals such as lead and mercury, certain foods and food additives, pesticides, industrial and/or cleaning solvents, and cosmetics. Even some naturally occurring substances can trigger the same effects. Symptoms may appear immediately after exposure or be delayed and may include limb weakness or numbness; loss of memory, vision, and/or intellect; headache; cognitive and behavioral problems; and sexual dysfunction. Individuals with certain disorders may be especially vulnerable to neurotoxins.

Local anesthesia in dentistry is common practice. Lidocaine, articaine, mepivacaine, prilocaine and in the

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USA bupivacaine and ropivacaine as well, are the amide anesthetic molecules used for dental local anesthesia. With thousands of people being anesthetized every day globally, the reports on adverse effects are very scarce. However, neurotoxicity has been a concern, as several authors have suggested that some of these local anesthetics can cause irreversible damage to nerves. A 2010 report by Garisto et al. [1], studied the reports received by the Food and Drug Administration Adverse Event Reporting System (FEARS) regarding paresthesia after dental local anesthesia, for the period from November 1997 till August 2008. The FEARS had received 248 reports of paresthesia occurring after dental procedures. In 94.5% of the cases, it involved a procedure that required a mandibular nerve block and in 89% of these cases, the lingual nerve was affected. They also noted that prilocaine 4% and articaine 4% were the most commonly used drugs in these events, which lead them to conclude that for mandibular nerve blocks, a concentration lower than 4% should be used. In 2015 a similar evaluation was published by Piccinni et al. [2], who looked at the FEARS reports between 2004 and 2011. They found that only 82 out of 528 reports with paresthesia or dysesthesia covered oral paresthesia. These 82 reports corresponded to 90 drug-reaction pairs: 37 articaine, 19 lidocaine, 14 prilocaine, 7 bupivacaine, and 13 others. Both articaine and prilocaine gave higher and significant signals in their study model. Articaine also gave a higher signal when any dental procedure was considered and an even higher signal if non-surgical procedures were considered. The last sentence of their abstract is interesting as they mention that among local anesthetics, only articaine and prilocaine generated sensations of paresthesia, especially when used in dentistry. The latter may hold the clue to the observation, namely that dental professionals may be using the wrong technique when administering a mandibular nerve block or that some events cannot be controlled: physical damage to the nerve caused by the needle, damage caused by pressure during injection, speed of injection, hemorrhage, perineural edema [2-10].

Reports of neurotoxic potential of dental local anesthetics seem controversial, hence the need to investigate the evidence from peer-reviewed publications. Many claims of neurotoxic effects of amides and esters used in local anesthesia are made on the basis of clinical experience, assumptions, and case reports. The aim of this narrative review was to assess the existing literature on neurotoxicity studies to search for objective evidence of cytotoxicity with regard to local anesthetic molecules used in dentistry.

MATERIAL AND METHODS

Fig. 1 displays the search terms that were used to facilitate the identification of publications in PubMed® database, as well as the number of publications that were produced from each search term, the number of publications that remained upon the application of exclusion criteria, and how many publications were deemed relevant after review by the researchers. The same terms shown in Fig. 1 were also used in the Google Scholar® database. However, all results overlapped with those from PubMed®. The following exclusion criteria were applied: publications published before 2009, publications not published in the English language, and case reports.

Initially, 2802 manuscripts were identified, which appeared to include 2,288 duplicates. The remaining 514 papers were subjected to the exclusion criteria, which resulted in the elimination of 435 more papers. A total of 79 full-text manuscripts were subsequently read by both researchers. The manuscripts were then itemized in consensus by both authors in an Excel spreadsheet (Microsoft®, Redmond, Washington, USA) identifying the study's country of origin and year of publication, the type of study (e.g. randomized clinical trial), presence of a control group, number of subjects if subjects were used in the study, whether or not the study had a connection to dentistry, and the conclusion of the study. Of these 79 manuscripts, the researchers found 23 manuscripts to be apposite to this study's aim.

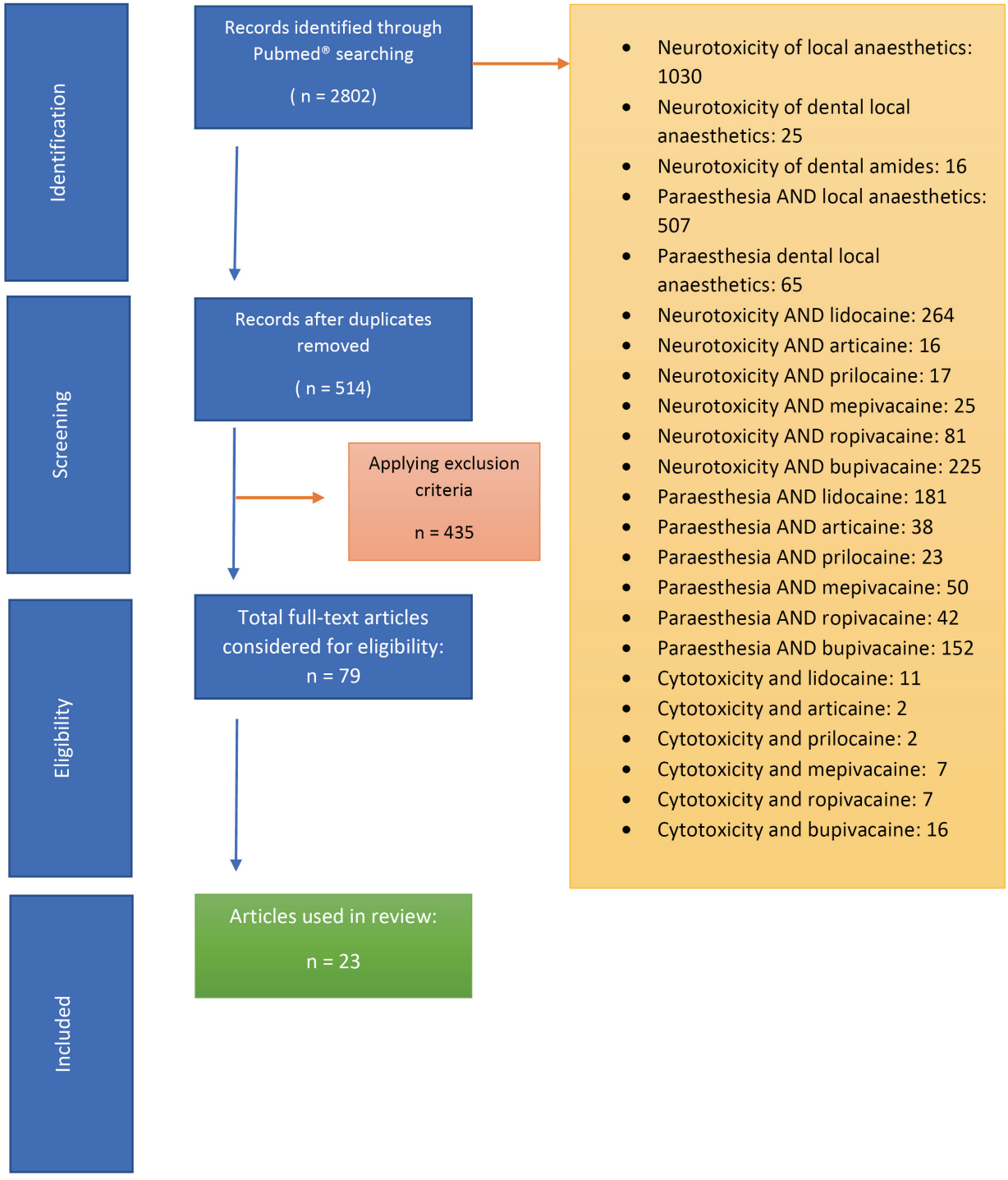

Fig. 1. PRISMA Flow Chart

RESULTS

The literature search resulted in the consideration of 17 *in vitro* studies and 3 reviews on *in vitro* studies eligible for the final review (Table 1). In Table 1 the *in vitro* studies are shown with a brief explanation of their materials and methods and a concise summary of the results and conclusions.

From Table 1, one can derive from the extreme right

Table 1. Summarized details of the papers used in this narrative review about neurotoxicity of local anesthetics

Title	Reference number, Authors, Country, year	Type of study	Material and methods condensed	Results and conclusions condensed
An early and lateofhuman oral mucosa fibroblasts.	[11] Oliveira et al., Spain, 2014	*In vitro*	mucosal fibroblasts	Lidocaine is able to alter cell viability (starting at 5% concentrations) and function (starting at 1% concentrations). Concentration of lidocaine had more impact than duration of exposure to lidocaine to cause cell apoptosis. Authors suggests to keep the concentration of lidocaine as low as possible in clinical situations.
Bupivacaine uncouples the mitochondrial oxidative phosphorylation, inhibits respiratory chain complexes I and III and enhances ROS production: results of a study on cell cultures.	[12] Cela et al., Italy, 2010	*In vitro*	4 different cell lines used: human hepatoma (HepG2), murine cardiomyoblasts (H9c2), murine skeletal myoblasts (L6), and primary normal dermal human fibroblasts (NDHF)	There was a dual dose- and time dependent effect of bupivacaine on the 4 different cell lines used in this study.
Bupivacaine,ropivacaine, and morphine: comparison of toxicity on human hamstring-derived stem/progenitor cells.	[13] Haasters et al., Germany, 2011	*In vitro*	hamstring cells	Bupivacaine (0.5% concentration) and ropivacaine (0.5 and 0.75% concentration) do not have a cytotoxic effect if they are less than 30 minutes in contact with the hamstring cells, but apoptosis was observed with both bupivacaine and ropivacaine. However, exposure of more than 6 hours leads to complete cell death.
Cell toxicity in fibroblasts, tenocytes, and human mesenchymal stem cells. A comparison of necrosis and apoptosis-inducing ability in ropivacaine, bupivacaine and triamcinolone.	[14] Zhang et al., Germany 2017	*In vitro*	human dermal fibroblasts, adipose-derived human mesenchymal stem cells, and tenocytes from rotator cuff tendon	Triamcinolone, ropivacaine and bupivacaine were tested at three different concentrations: 0.5%, 0.25% and 0.125%. Bupivacaine showed a concentration related necrosis-inducing effects on fibroblasts and tenocytes, but not on mesenchymal stem cells. There were no differences between the local anesthetic agents used and the between the cell lines with regard to cell apoptosis. Ropivacaine causes less cell necrosis than bupivacaine.
Cytotoxic effects of local anesthesia through lidocaine/ropivacaine on human melanoma cell lines.	[15] Kang et al., China, 2016	*In vitro*	human melanoma cell lines	Melphalan (nitrogen mustard alkylating agent) was used as a control agent for comparison of cytotoxic activity. Flow-cytometry was used to verify cell viability after exposure to lidocaine (2% concentration), ropivacaine (0.75% concentration) or a combination of lidocaine and ropivacaine. It was found that lidocaine, ropivacaine and/or lidocaine-ropivacaine combined resulted in detrimental cytotoxicity, which was both time- and concentration dependent.
Cytotoxic effects ofbupivacaine, and lidocaine on rotator cuff tenofibroblasts.	[16] Sung et al., Korea, 2014	*In vitro*	rotator cuff tenofibroblasts	Twelve possible local anesthetic concentrations were used: 0.02%, 0.2%, 0.075% and 0.75% ropivacaine, 0.025%, 0.25%, 0.05% and 0.5% bupivacaine and 0.1%, 1% , 0.02% and 2% lidocaine. The exposure times were 5, 10, 20, 40 and 60 minutes for the anesthetic originalconcentrations and 2, 6, 12, 24, 48 and 72 hours for the 10% diluted concentrations. All were tested at 4 pH levels (7.4, 6.0 and 4.4). It was found that ropivacaine and bupivacaine caused significant decreased cell viability with increasing concentration and exposure time. Lidocaine, however, was highly cytotoxic even in low concentrations.Ropivacaine 0.2% was the least cytotoxic agent tested in this study. The authors conclude that for tenofibroblasts 0.2% ropivacaine is the least cytotoxic and that in general of the 3 tested amino-amides, the cytotoxicity increases with increasing concentration of the local anesthetic.
Cytotoxicity and type of cell death induced by local anesthetics in human oral normal and tumor cells.	[17] Kobayashi et al., Japan, 2012	*In vitro*	normal cell lines and oral squamous cell carcinoma cell lines	All local anesthetics (dibucaine, tetracaine, bupivacaine, lidocaine, procaine and mepivacaine) showed slightly higher cytotoxicity towards oral squamous cell carcinoma (OSCC) cell lines than towards normal oral cells. Dibucaine was the most cytotoxic, followed by tetracaine, bupivacaine or ethylaminobenzoate, whereas lidocaine, procaine and mepivacaine were much less cytotoxic.

Cytotoxicity of local anesthetics on human mesenchymal stem cells *in vitro.*	[18] Breu et al., Germany, 2013	*In vitro*	mesenchymal stem cells	Mesenchymal stem cells were exposed to preservative free bupivacaine (0.03125%, 0.0625%, 0.125%, 0.25% and 0.5%), ropivacaine (0.03125%, 0.0625%, 0.125%, 0.25%, 0.5% and 0.75%) and mepivacaine (0.03125%, 0.0625%, 0.125%, 0.25%, 0.5%, 1% and 2%) for 1 hour. Flow cytometry and staining were used as tests to assess cell viability, apoptosis and necrosis. All three local anesthetics were cytotoxic in concentration and time specific manner. Ropivacaine was the least cytotoxic aminoamide anesthetic.
Cytotoxicity of local anesthetics on human mesenchymal stem cells.	[19] Rahnama et al., USA, 2013	*In vitro*	human mesenchymal stem cells	Human mesenchymal stem cells were exposed for 1 hour to lidocaine (1 and 2% concentrations), bupivacaine (0.25 and 0.5% concentrations), and ropivacaine (0.2 and 0.5% concentrations). The cells were assessed after 24 hours. Lidocaine 2% showed the highest toxic effect of all tested agents and concentrations. Between bupivacaine and ropivacaine, no significant differences were noticed with regard to cell toxicity.The latter did not show a difference either with control cells. The authors conclude that for intra-articular anesthesia, bupivacaine and ropivacaine are to be preferred.
Effects oflidocainetorn rotator cuff tendons.	[20] Honda et al., Japan, 2016	*In vitro* and *in vivo*	rat study on rotator cuff tendons - lidocaine injection in one shoulder and saline in contralateral shoulder and human rotator cuff tenocytes from 14 patients (9 males and 5 females)	Lidocaine (0.0001, 0.01, 0.05 and 0.1% concentrations), compared to saline, caused cytotoxicity to tenocytes, decreased biomechanical properties, and induced apoptosis and delay of collagen organization.
Lipophilicity but not stereospecificity is a major determinant of local anesthetic-induced cytotoxicity in human T-lymphoma cells.	[21] Werdehausen et al., Germany, 2012	*In vitro*	T-lymphoma cells incubated with 8 different local anesthetics	Concentration-dependent cytotoxicity was observed for all 8 investigated local anesthetics. Apoptosis was seen at low concentrations, whereas necrosis was observed at higher concentrations. In order of decreasing toxicity, the 8 local anesthetics, 2 esters and 6 aminoamides, can be ranked as tetracaine (ester), bupivacaine, ropivacaine, prilocaine, procaine (ester), lidocaine, articaine and mepivacaine. Moderate correlations for cytotoxicity with lipophilicity and clinical potency of local anesthetics can be found in non-neuronal cells that are less thanthose reported previously with neuronal cells. Structural factors such as ester or amide linkage or stereospecificity do not have any influence on cytotoxicity.
Local anesthetichuman mesenchymal stem cells during chondrogenic differentiation.	[22] Breu et al., Germany, 2015	*In vitro*	human mesenchymal stem cells	One hour exposure to bupivacaine, ropivacaine and mepivacaine leads to cytotoxicity in mesenchymal stem cells that are undergoing chondrogenesis. Bupivacaine, ropivacaine and mepivacaine did not differ in in cytotoxicity of the mesenchymal stem cells in aggregate cultures. The authors warn for the use of these local anesthetics in cartilage repair procedures.
The Cytotoxicity of Bupivacaine, Ropivacaine, and Mepivacaine on Human Chondrocytes and Cartilage	[23] Breu et al., Germany, 2013	*In vitro*	human articular chondrocytes exposed to bupivacaine, ropivacaine and mepivacaine for 1 hour	Flow cytometry, staining and caspase detection were used to assess the chondrocytes' viability, apoptosis and necrosis. Chondrotoxic effects increased from ropivacaine to mepivacaine to bupivacaine in a time-dependent, and concentration-dependent manner.Chondrotoxicity was not correlated with potency of the studied local anesthetics.
The effect of Lidocaine on the viability of cultivated mature human cartilage cells: an *in vitro* study.	[24] Jacobs et al., Belgium, 2011	*In vitro*	human articular chondrocytes exposed to lidocaine 1 and 2%, with and without epinephrine, for 1 hour	Lidocaine is significantly more toxic to human chondrocyte cells than saline.Caution is recommended with clinical use of intra-articular lidocaine.
Cytotoxicity of Local Anesthetics in Human Neuronal Cells	[25] Perez-Castro et al., USA, 2009	*In vitro*	human SH-SY5Y neuroblastoma cells were exposed to bupivacaine, ropivacaine, mepivacaine, lidocaine, procaine, and chloroprocaine	Ten minute exposure to any of the 6 tested local anesthetics, resulted in decreased cell viability in a concentration dependent manner. In increasing order of killing potency: procaine, mepivacaine, lidocaine, chloroprocaine, ropivacaine and bupivacaine. Only bupivacaine and lidocaine killed all cells with increasing concentration. The authors mentioned that although

				lidocaine is linked to the highest incidence of transient neurological symptoms, it was not the most toxic local anesthetic tested in their study. Bupivacaine, however, a drug causing a very low incidence of transient neurological symptoms, was the most toxic local anesthetic in their model.
The Comparative Cytotoxic Effects of Different Local Anesthetics on a Human Neuroblastoma Cell Line	[26] Malet et al., France, 2015	*In vitro*	human SH-SY5Y neuroblastoma cells were exposed to ropivacaine, mepivacaine, lidocaine, articaine, bupivacaine, and prilocaine	After 20 minutes of treatment, all 6 local anesthetic agents were found to be neurotoxic in a concentration-dependent manner. Ropivacaine and articaine were found to be the least neurotoxic of the tested local anesthetics. In increasing order of neurotoxicity the other local anesthetics are mepivacaine, prilocaine, lidocaine and bupivacaine. The latter having the highest neurotoxic effect. Therefore the authors conclude that among dental local anesthetics, articaine is the least neurotoxic.
Effects of Lidocaine and Articaine on Neuronal Survival and Recovery	[27] Albalawi et al., USA, 2017	*In vitro*	human neural SH-SY5Y cells were exposed to 4% articaine and 2% lidocaine, both with 1:100,000 epinephrine, for 5 minutes	Articaine does not damage neural cells more than does lidocaine.This *in vitro* study concludes that there is no difference between lidocaine 2% and articaine 4% with regards to neurotoxicity.
Single-dose local anesthetics exhibit a type-, dose-, and time-dependent chondrotoxic effect on chondrocytes and cartilage: a systematic review of the current literature	[28] Kreuz et al., Germany, 2018	Review		The cytotoxicity of local anesthetics on chondrocytes is dependent on dose, time, and type of local anesthetics. Single-dose intra-articular administration of local anesthetics impede chondrocyte metabolism and should be performed only with low concentrations for selected diagnostic purposes and painful joints. Bupivacaine and lidocaine were found to be more chondrotoxic than mepivacaine and ropivacaine. Lidocaine was found to be chondrotoxic at any concentration and therefore should not be used for single shot intra-articular injections.
Articaine and neurotoxicity – A Review	[29] Hopman et al., The Netherlands, 2017	Review		All local anesthetics are potentially neurotoxic. In rare cases paresthesia may occur. The authors mention that clinical studies from some countries, seem to associate articaine with paresthesia. However, animal models have not shown a higher neurotoxic effect from articaine, compared to other amide anesthetics.
Cytotoxicity of Local Anesthetics in Mesenchymal Stem Cells.	[30] Wu et al., USA, 2018	Review		Lidocaine, ropivacaine, mepivacaine, bupivacaine, articaine and prilocainehave all been tested *in vitro* with mesenchymal stem cell lines and all seem to be associated with concentration and time dependent effects on cell viability of mesenchymal stem cells. Ropivacaine seems to be the least cytotoxic of all. The authors also suggest that in vivo studies are required to understand the interactions of these agents with mesenchymal stem cells, as *in vitro* studies lack the pharmacokinetics of anesthetics or the recovery of the stem cells in their natural environment.

column that there is no consensus among the results with regard to which amide or ester is more neurotoxic. Thirteen of the 17 *in vitro* studies investigated the impact on the cell line by the concentration of the anesthetic, while in 8 the time of contact of the anesthetic with the cells under investigation was taken into account. In 5 studies both the concentration and the exposure contact time were investigated.

There was also a substantial heterogeneity of the studied anesthetics and comparisons of anesthetics in these 17 *in vitro* papers: lidocaine (10 studies), prilocaine (2 studies), mepivacaine (7 studies), articaine (3 studies), bupivacaine (12 studies), ropivacaine (12 studies), tetracaine (2 studies), procaine (2 studies), dibucaine (1 study), and chloroprocaine (1 study). Besides this anesthetic molecule heterogeneity, another was observed, namely that 12 different cell lines were used in these 17 *in vitro* studies, with fibroblasts being the most common cell lines (6/17 studies) used, followed by mesenchymal stem cells (4/17 studies) (Table 1).

Three additional papers (Table 2) were identified as audits (FDA Adverse Event Reporting System), of which two were specifically about dental situations where paresthesia was the result of a dental anesthesia procedure

Table 2. Summarized details of the papers analyzing reports about neurotoxicity of local anesthetics

	Reference number, Authors, Country, Year	Material and methods condensed	Results an conclusions condensed
Occurrence of paresthesia after dental local anesthetic administration in the United States	[1] Garisto et al., USA, 2010	Analysis of reports of paresthesia involving dental local anesthesia received by the FDA Adverse Event reporting System (FEARS) between November 1997 and August 2008	In a total of 248 cases of paresthesia, 94.5% were associated with mandibular nerve blocks. The lingual nerve was affected in 89% of these cases. The authors found that 4% prilocaine and 4% articaine were the most often associated local anesthetic agents involved in these reports. The authors claim that these results suggest that paresthesia occurs more commonly after use of 4% local anesthetic solutions. They therefore recommend to consider local anesthetics with less than 4% concentration for inferior alveolar nerve blocks.
Paresthesia after local anesthetics: an analysis of reports to the FDA adverse event reporting system	[2] Piccinni et al., Italy, 2015	Evaluate alert signals of paresthesia by dental local anesthetics, as recorded by the FDA Adverse Event Reporting System (FEARS) between 2004 and 2011	A total of 528 reports were found that concerned 'paresthesias and dysesthesias'. They consisted of 573 drug-reaction pairs, consisting of 247 lidocaine, 99 bupivacaine, 85 articaine, 30 prilocaine, and 112 others. The signal was significant only for articaine and prilocaine. Analysis of the specific term "Oral Paresthesia" resulted in 82 reports, which corresponded to 90 drug-reaction pairs (37 articaine, 19 lidocaine, 14 prilocaine, 7 bupivacaine, and 13 others) and again confirmed the signal for articaine and prilocaine. The analysis of reports concerning dental procedures retrieved a signal for articaine, both for any procedures and for nonsurgical ones. The authors conclude that among local anesthetics, only articaine and prilocaine generated a signal of paresthesia, especially when used in dentistry.
Preliminary results of the Australasian Regional Anesthesia Collaboration: a prospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications.	[31] Barrington et al., Australia, 2009	Audit of 6950 patients who received 8189 peripheral nerve or plexus blocks (not dental) - 6069 patients were followed up successfully	Only 0,5% of the patients (n=30) required referral for neurologic assessment. Only 3 of these 30 patients had a block-related nerve injury (or 0.04% prevalence of nerve damage for peripheral nerve blocks). Systemic toxicity as a complication occurs in approximately 1% of peripheral nerve blocks. The incidence of serious complications after peripheral nerve blockade is uncommon and the origin of neurologic symptoms/signs in the postoperative period is most likely to be unrelated to nerve blockade.

and where neurotoxicity was assumed. Garisto et al. suggested that it is safer to perform local anesthesia with an anesthetic with a concentration below 4%. The latter refers to articaine and prilocaine [1]. In a 2015 audit, also performed on data from the FDA Adverse Event Reporting System, Piccini et al. concluded that articaine and prilocaine are associated with a greater incidence of paresthesia when used in dentistry [2]. Table 2 shows the condensed details, results, and conclusions of these audit papers. The Australasian Regional Anesthesia Collaboration audit [31] is not specific on dental anesthesia adverse effects but stated that serious complications after peripheral nerve blocks are unusual, and that neurologic symptoms are unlikely to be related to the nerve blockade.

DISCUSSION

Paresthesia, as a complication of local (peripheral) anesthesia, does not necessarily imply neurotoxicity of the local anesthetic. In a previous review by our group [32] regarding the efficacy of local anesthetics in dentistry, it was found that none of the local anesthetics used is 100% successful in dentistry. We mentioned the possible reason for that being the technique of administering the local anesthetic (e.g. mandibular nerve block). The results of the current review cannot rule out physical damage to the nerves (intrafascicular injection) for the paresthetic symptoms observed in the clinical situation, but rather point in the direction of the concentration of the anesthetics used. The overall conclusion that can be derived from all the studies implemented in this narrative review is that all local anesthetics are potentially cytotoxic in one way or another and that the consensus among researchers is that the lower the dosage can be kept, the better. Articaine (4% concentration), in particular, has been pointed out in several reports as being potentially neurotoxic [1-6,32, 33], while several others have reported it as being the

best anesthetic as it is more fat-soluble than other amide molecules [34-36]. Possibly the thiophene ring in articaine, as opposed to the benzene ring in other amide anesthetics, and its being marketed as a 4% solution, play an important role in its potential neurotoxic effect, as alcohol molecules can be formed which can damage the neurons. However, the latter is not proven in animal studies and in several *in vitro* studies [29].

The heterogeneity in the methodology of the studies we found, illustrates the need for more focused and standardized research on the potential neurotoxic effects of local anesthetics used in dentistry. The variety of the combinations of anesthetics used in the studies, their various concentrations and the myriad of cell lines used to study the effects of local anesthetic molecules, make comparisons between studies very difficult and complicated. Nevertheless, the conclusion one can derive from these studies is that all local anesthetics are potentially neurotoxic and that the higher their concentration, the higher the neurotoxic effect will be [11-29]. In some studies, though, the emphasis was more on the exposure time of cell lines to an anesthetic molecule [12-16,18, 22-24]. There appears to be one consensus, namely that 4% solutions should be avoided in dentistry if possible. However, more specific studies on human neural cell lines and in particular on the Trigeminal nerve, would be welcome to investigate the potential differences between the nerve branches (e.g. Lingual nerve versus the Maxillary nerve) as they may differ in their fasciculi [29].

Persistent paresthesia initiated by local anesthetics is estimated to range from 1:160,571 to 1:4,156,848 [29]. The causes associated with persistent paresthesia are high concentration of anesthetics, intrafascicular injections, direct needle damage, high pressure during injection, formation of oxygen radicals, surgical interventions (e.g. third molar removal), and infection or degenerative diseases [29]. Interestingly reports regarding transient or permanent paresthesia after mandibular block anesthesia are more common than reports about paresthesia after buccal infiltrations in either the mandible or the maxilla. The former usually involves damage to the lingual nerve branch of the mandibular nerve (V.b). It is believed that this can be associated with the fact that the lingual nerve has fewer fascicles than the inferior nerve itself. It may be even unifascicular in about 30% of patients [2,29,37].

It is interesting that two studies [1,2] used the same database (FDA Adverse Event Reporting System), but that different results were found because different search queries to identify adverse effects from dental local anesthesia were used. That observation was also made by Hopman et al. [29], and illustrates the importance of assessing studies carefully and to interpret the results wisely before translating the findings to a clinical situation.

We can conclude that further investigations into the potential neurotoxicity of local anesthetics and the mechanisms involved are paramount. For the time being, the consensus appears to be to use injectable anesthetics in dentistry with a concentration below 4%, although the latter statement is not 100% based on firm evidence [1,2, 11,12,14-16,18-21,23-27,29].

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AUTHOR CONTRIBUTIONS

Johan Aps: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing
Nelly Badr: Data curation, Formal analysis, Project administration, Writing - review & editing

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REFERENCES

1. Garisto GA, Gaffen AS, Lawrence HP, Tenenbaum HC, Haas DA. Occurrence of paresthesia after dental local anesthetic administration in the United States. J Am Dent

Assoc 2010; 141: 836-44.
2. Piccinni C, Gissi DB, Gabusi A, Montebugnoli L, Poluzzi E. Paraesthesia after local anaesthetics: an analysis of reports to the FDA Adverse Event Reporting System. Basic Clin Pharmacol Toxicol 2015; 117: 52-6.
3. Haas DA, Lennon D. A 21 year retrospective study of reports of paresthesia following local anesthetic administration. J Can Dent Assoc 1995; 61: 319-20.
4. Pogrel MA. Permanent nerve damage from inferior alveolar nerve blocks: a current update. J Calif Dent Assoc 2012; 40: 795-7.
5. Dower JS Jr. A review of paresthesia in association with administration of local anesthesia. Dent Today 2003; 22: 64-9.
6. Hillerup S, Jensen R. Nerve injury caused by mandibular block analgesia. Int J Oral Maxillofac Surg 2006; 35: 437-43.
7. Malamed SF. Local anesthetics: dentistry's most important drugs, clinical update 2006. J Calif Dent Assoc 2006; 34: 971-6.
8. Peltier B, Dower JS Jr. The ethics of adopting a new drug: articaine as an example. J Am Coll Dent 2006; 73: 11-20.
9. Haas DA. Localized complications from local anesthesia. J Calif Dent Assoc 1998; 26: 677-82.
10. Haas DA. Articaine and paresthesia: epidemiological studies. J Am Coll Dent 2006; 73: 5-10.
11. Oliveira AC, Rodríguez IÁ, Garzón I, Martín-Piedra MÁ, Alfonso-Rodríguez CA, García JM, et al. An early and late cytotoxicity evaluation of lidocaine on human oral mucosa fibroblasts. Exp Biol Med 2014; 239: 71-82.
12. Cela O, Piccoli C, Scrima R, Quarato G, Marolla A, Cinnella G, et al. Bupivacaine uncouples the mitochondrial oxidative phosphorylation, inhibits respiratory chain complexes I and III and enhances ROS production: results of a study in cell cultures. Mitochondrion 2010; 10: 487-96.
13. Haasters F, Polzer H, Prall WC, Saller MM, Kohler J, Grote S, et al. Bupivacaine, ropivacaine, and morphine: comparison of toxicity on human hamstring-derived stem/progenitor cells. Knee Surg Sports Traumatol Arthosc 2011; 19: 2138-44.
14. Zhang AZ, Ficklscherer A, Gülecyüz MF, Paulus AC, Niethammer TR, Jansson V, et al. Cell toxicity in fibroblasts, tenocytes, and human mesenchymal stem cells – a comparison of necrosis and apoptosis-inducing ability in ropivacaine, bupivacaine and triamcinolone. Arthroscopy 2017; 33: 840-8.
15. Kang DK, Zhao LY, Wang HL. Cytotoxic effects of local anesthesia through lidocaine/ropivacaine on human melanoma cell lines. Braz J Anesthesiol 2016; 66: 594-602.
16. Sung CM, Hah YS, Kim JS, Nam JB, Kim RJ, Lee SJ, et al. Cytotoxic effects of ropivacaine, bupivacaine and lidocaine on rotator cuff tenofibroblasts. Am J Sports Med 2014; 42: 2888-96.
17. Kobayashi K, Ohno S, Uchida S, Amano O, Sakagami H, Nagasaka H. Cytotoxicity and type of cell death induced by local anesthetics in human oral normal and tumor cells. Anticancer Res 2012; 32: 2925-33.
18. Breu A, Eckl S, Zink W, Kujat R, Angele P. Cytotoxicity of local anesthetics on human mesenchymal stem cells in vitro. Arthroscopy 2013; 29: 1676-84.
19. Rahnama R, Wang M, Dang AC, Kim HT, Kuo AC. Cytotoxicity of local anesthetics in human mesenchymal stem cells. J Bone Joint Surg Am 2013; 95: 132-7.
20. Honda H, Gotoh M, Kanazawa T, Nakamura H, Ohta K, Nakamura K, et al. Effects of lidocaine on torn rotator cuff tendons. J Orthop Res 2016; 34: 1620-7.
21. Werdehausen R, Braun S, Fazeli S, Hermanns H, Hollmann MW, Bauer I, et al. Lipophilicity but not stereospecificity is a major determinant of local anesthetic- induced cytotoxicity in human T-lymphoma cells. Eur J Anaesthesiol 2012; 29: 35-41.
22. Breu A, Scheidhammer I, Kujat R, Graf B, Angele P. Local anesthetic cytotoxicity on human mesenchymal stem cells during chondrogenic differentiation. Knee Surg Sports Traumatol Arthrosc 2015; 23: 937-45.
23. Breu A, Rosenmeier K, Kujat R, Angele P, Zink W. The cytotoxicity of bupivacaine, ropivacaine and mepivacaine on human chondrocytes and cartilage. Anesth Analg 2013; 117: 514-22.
24. Jacobs TF, Vansintjan PS, Roels N, Herregods SS, Verbruggen G, Herregods LL, et al. The effect of lidocaine on the viability of cultivated mature human cartilage cells:

an in vitri study. Knee Surg Sports Arthroasc 2011; 19: 1206-13.
25. Perez-Castro R, Patel S, Garavito-Aguilar ZV, Rosenberg A, Recio-Pinto E, Zhang J, et al. Cytotoxicity of local anesthetics in human neuronal cells. Anesth Analg 2009; 108: 997-1007.
26. Malet A, Faure MO, Delatage N, Pereira B, Haas J, Lambert G. The comparative cytotoxic effects of different local anesthetics on human neuroblastoma cell line. Anesth Analg 2015; 120: 589-96.
27. Albalawi F, Lim JC, DiRenzo KV, Hersch EV, Mitchell CH. Effects of lidocaine and articaine on neuronal survival and recovery. Anesth Prog 2018; 65: 82-8.
28. Kreuz PC, Steinwachs M, Angele P. Single-dose local anesthetics exhibit a type-, dose-, and time-dependent chondrotoxic effect on chondrocytes and cartilage: a systematic review of the current literature. Knee Surh Sports Arthrosc 2018; 26: 819-30.
29. Hopman AJG, Baart JA, Brand HS. Articaine and neurotoxicity − a review. Br Dent J 2017; 223: 501-6.
30. Wu T, Smith J, Nie H, Wang Z, Erwin PJ, van Wijnen AJ, et al. Cytotoxicity of local anesthetics in mesenchymal stem cells. Am J Phys Med Rehabil 2018; 97: 50-5.
31. Barrington MJ, Watts SA, Gledhill SR, Thomas RD, Said SA, Snyder GL, et al. Preliminary results of the Australasian regional anesthesia collaboration. A retrospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications. Reg Anesth Pain Med 2009; 34: 534-41.
32. Badr N, Aps J. Efficacy of dental local anesthetics: a review. J Dent Anesth Pain Med 2018; 18: 319-32.
33. Hillerup S, Jensen RH, Ersboll BK. Trigeminal nerve injury associated with injection of local anesthetics: needle lesion or neurotoxicity? J Am Dent Assoc 2011; 142: 531-9.
34. Martin M, Nusstein J, Drum M, Reader A, Beck M. Anesthetic efficacy of 1.8 mL versus 3.6 mL of 4% articaine with 1:100,000 epinephrine as a primary buccal infiltration of the mandibular first molar. J Endod 2011; 37: 588-92.
35. Nydegger B, Nusstein J, Reader A, Drum M, Beck M. Anesthetic comparisons of 4% concentrations of articaine, lidocaine, and prilocaine as primary buccal infiltrations of the mandibular first molar: a prospective randomized, double-blind study. J Endod 2014; 40: 1912-6.
36. Kämmerer PW, Schneider D, Palarie V, Schiegnitz E, Daubländer M. Comparison of anesthetic efficacy of 2 and 4% articaine in inferior alveolar nerve block for tooth extraction − a double-blind randomized clinical trial. Clin Oral Investig 2017; 21: 397-403.
37. Pogrel MA, Schmidt BL, Sambajon V, Jordan RC. Lingual nerve damage due to inferior alveolar nerve blocks: a possible explanation. J Am Dent Assoc 2003; 134: 195-9.