Local is “lekker”

C Quan

Department of Anaesthesia, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, South Africa
Corresponding author, email: barrowceleste@gmail.com

Summary
Local anaesthetics agents (LAA) are used ubiquitously in the medical field and in a wide variety of ways: tissue infiltration, perineural, intra-articular and intravenous. The purpose of this review is to explore the pharmacology of LAAs and to examine the clinical applications for LAAs.

Keywords: local anaesthetic agents, pharmacology, clinical applications

Definition
LAAs are sodium (Na+) channel blockers. They can be used as:
- Local anaesthetic agents for topical, regional and neuraxial nerve conduction blockade.
- Antidysrhythmics by affecting the Na+ ion movement and affecting the action potential of cardiac tissue.
- Anti-epileptics.

Classification
- LAAs can be divided into two groups by the type of bond between the benzene ring and the tertiary amide:
  - Amides
  - Esters

Table I: Classification of local anaesthetics

| Amides          | Esters          |
|-----------------|-----------------|
| Lignocaine      | Cocaine         |
| Bupivacaine     | Benzocaine      |
| Levobupivacaine | Tetracaine      |
| Ropivacaine     | Procaine        |
| Prilocaine      | Amethocaine     |

Metabolised: hepatic microsomal enzyme system
Metabolised: plasma cholinesterase

Mechanism of action

Na+ channel blockade
- LAAs have to diffuse through the nerve sheath and bind to the intracellular portion of voltage-gated Na+ channels.1
- Only the non-ionised form of the drug can cross the cell membrane.1
- LAAs bind to the S6 segment of the fourth homologous domain of the Na+ channel.1
- The order of affinity of LAAs for different Na+ channel states is more with open > inactivated > resting.2
- When the LAA binds to the Na+ channel it prevents the influx of Na+, depolarisation and impulse propagation.1

Other ion channel involvement1
- Potassium (K+) and calcium (Ca2+) channels may also be blocked.

Receptor involvement1
- Gq protein-coupled receptors may be blocked by local anaesthetics, suggesting an intracellular target for the anti-inflammatory effects of local anaesthetic drugs.

Transient receptor potential vanilloid subtype-1 channels1
- Permanently charged local anaesthetic agents may gain entry into a cell via the transient receptor potential vanilloid subtype-1 channels (TRPV-1).
- Once opened, these channels non-selectively let through mono- and divalent cations, as well as anonymous large charged molecules.
- Once these channels are opened, a more potent and prolonged impulse is produced.
- Capsaicin and heat are TRPV-1 openers and enhance the entry of charged local anaesthetic compounds.

Structure-activity relationships1

Chemical structure
Modification of the basic local anaesthetic structure will change the characteristics of these drugs (lipid solubility, duration of onset, duration of action, rate of metabolism and potency).
Lipid solubility

- Higher lipid solubility speeds up crossing of the membrane, but also results in increased sequestration of non-ionised drugs into the myelin sheaths and other lipid compartments.
- The net result is a slower onset but increased duration of action (because of local anaesthetic stored in lipid tissue).
- Lipid solubility also confers a higher potency because of:
  - The higher concentration gradient across the membrane driving more of the drug intracellularly.
  - The increased affinity of the more lipid-soluble drug for the Na⁺ channel.
  - The ability to alter the conformation of the Na⁺ channel by direct effects on the lipid membrane.

Protein binding

- Increased protein binding is associated with increased duration of activity.
- This is related to the degree of protein binding onto extracellular and membranous proteins.

pKa

- pKa is the pH value of a substance at which equal concentrations of acid and its conjugate base forms are present.
- The closer the pKa is to normal pH, the more the drug exists in its unionised form, the faster it crosses into the nerve and the faster the onset of action.

Isomerism

- Definitions
  - Isomers (noun): two or more compounds that contain the same number of atoms of the same elements but differ in structural arrangement and properties.
  - Chiral (adjective): an object is chiral if it is distinguishable from its mirror image but cannot be superimposed.
  - Enantiomers (noun): are chiral molecules that are mirror images of one another. The molecules are non-superimposable on one another.
  - Racemic (adjective): a mixture that has equal amounts of left- and right-handed enantiomers of a chiral molecule.
- All currently available local anaesthetics, except for lignocaine, are racemic mixtures. Ropivacaine and levobupivacaine contain only S-enantiomer.
- R-enantiomers seem to have greater potency for conduction block in cardiac and neural tissues and may have greater therapeutic efficacy and potential systemic toxicity.

Nerve anatomy

- Nerve anatomy and frequency of stimulation of a specific nerve also influence the action and the potency of local anaesthetic drugs.
- Higher activity nerves are easier to block.
- Myelinated nerves are, in theory, easier to block as the local anaesthetic needs only to inhibit salutatory conduction through the nodes of Ranvier, which are smaller areas to penetrate and block.
- Smaller-diameter myelinated nerves (B fibre-type nerves), responsible for pre-ganglionic autonomic conduction, are the most sensitive to local anaesthetics.
- In thicker nerve fibres, the presence of A α (motor) and A β (pressure and proprioception) fibres with long intermodal distances and a reduced number of nodes makes large nerves more difficult to block.

Regional blood flow

- Regional blood flow in the area of blockade will determine the rate of uptake of local anaesthetic drug into the systemic circulation.
- Higher blood flow assists removal of drug from the area and shortens the duration of action, but it also increases the chance of local anaesthetic systemic toxicity (LAST), as the systemic concentration will rise more rapidly.
- Vasoconstriction, either due to the inherent effect of the local anaesthetic or due to the addition of adrenaline, prevents this.

Patient factors

- Hyperkalaemia causes an increase in resting membrane potential, and thereby an increase in inactive receptors. This may increase local anaesthetic toxicity.
- Low pH in tissues may delay absorption.
- Neonates have lower levels of α 1-acid glycoprotein, thus increasing the free fraction of LAAs.
- Hepatic impairment decreases the metabolism of amide LAAs.
- Pregnancy has the following effects:
  - Less plasma protein, therefore more rapid onset of block.
  - Progesterone increases sensitivity to LAAs.
  - Epidural veins become engorged during pregnancy which increases absorption and increases the risk of cardiovascular toxicity.
LAAs cross the placenta. This is governed by maternal free
drug concentration, ionisation and metabolism of the
drug by the mother. The lower fetal pH may also cause ion
trapping.

Table III: Physicochemical properties of local anaesthetics

| Property          | Effect                                           |
|-------------------|--------------------------------------------------|
| pKa               | The closer the pKa is to normal pH, the faster the onset of action |
| Lipid solubility  | Higher lipid solubility = slower onset of action Higher solubility = increased potency |
| Protein binding   | Higher protein binding = prolonged effect         |
| Isomerism         | L (S) enantiomers = less potent, less toxic       |
| Nerve anatomy     | Smaller diameter = easier blockade Myelinated = easier blockade Increased activity = easier blockade |
| Local factors     | Sites of injection (peripheral vs neuraxial) Increased local blood flow = decreased duration of activity Addition of vasoconstrictors = decreased onset time and increased duration of action |

Pharmacokinetics

Absorption

Decreased systemic absorption leads to a greater margin of safety in clinical use. Factors that determine rate of absorption and extent of systemic toxicity include:

- Site of injection: Rates of absorption decrease in the following order intrapleural > intercostal > caudal > lumbar epidural > brachial plexus > sciatic or femoral nerve > subcutaneous tissue.
- Total dose.
- LAA with higher lipid solubility and greater protein binding have lower systemic absorption.
- Adrenaline: the addition of adrenaline is only effective in agents that exhibit lower lipid solubility, shorter duration of action and lower potency.

Distribution

Distribution depends on:

- Organ perfusion: the “vessel-rich” organs have the fastest uptake of drug. LAST manifests first in the brain and the heart.
- Drug-partition coefficient: Tissue/blood partition coefficients are influenced by protein-binding (which retains local anaesthetic in the blood) and lipid solubility (which facilitates uptake). Muscle provides the biggest reservoir for agents because of its large mass.
- Plasma protein binding.

Elimination

- Amides undergo hepatic metabolism (cytochrome P450).
- Esters are metabolised by plasma cholinesterase.
- The metabolism of prilocaine produces o-toluidine, which in high concentrations or in relative deficiency of methaemoglobin reductase will oxidise normal haemoglobin to cause methaemoglobinaemia.

LAST

Incidence

- 0.03%
- Evolution of local anaesthetic (LA) techniques such as high-volume fascial plane blocks, continuous catheter techniques, employing multiple LAA techniques in the same patient and tumescent anaesthesia all contribute to the ongoing risks of LAST.

Table IV: Maximum doses of local anaesthetics

| Drug          | Maximum dose                      |
|---------------|-----------------------------------|
|               | Without adrenaline | With adrenaline |
| Bupivacaine   | 2 mg/kg                | No benefit       |
| Ropivacaine   | 2 mg/kg                | No benefit       |
| L-bupivacaine | 2 mg/kg                | No benefit       |
| Lignocaine    | IV 1–1.5 mg/kg          | Not applicable   |
|               | SC or IM 3–5 mg/kg       | 7 mg/kg          |
|               | Topical 5 mg/kg          | Not applicable   |
| Cocaine       | 1.5 mg/kg               | Not applicable   |

Clinical signs and symptoms of toxicity

LAST is a consequence of Na⁺, K⁺ and Ca²⁺ channel blockade, disruption in metabolic signalling as well as inhibition of oxidative phosphorylation. This impacts negatively on myocardial contractility, conduction and systemic vascular resistance. The central nervous system manifestations are mainly due to ionic channel malfunction.

Factors that increase the likelihood of LAST

- Extremes of age
- Low muscle mass
- Female
- Pregnancy
- Underlying cardiac disease (low ejection fraction, arrhythmias, conduction abnormalities)
• Liver disease
• Renal disease
• Central nervous system disease
• Metabolic disease (diabetes, isovaleric acidaemia, mitochondrial disease and carnitine deficiency)
• LAA characteristic
  ◦ Bupivacaine has a lower safety margin
  ◦ Block site
  ◦ Infusions
• Practice setting
  ◦ Up to 20% of LAST occur outside the hospital setting
  ◦ Non-anaesthesiologists are involved in 50% of LAST cases

Risk reduction
• Use the least dose of LAA necessary to achieve the extent and duration of the block.
• Use ultrasound (increased accuracy of delivery permits reduction in dose of LAA, vascular puncture is reduced and visual cues signalling intravascular injection allow for early termination).  
• Fractionated injection of LAA in aliquots of less than 5 ml, pausing for 30–45 seconds between injections and aspirating before the next injection.  
• Consider using a marker such as adrenaline 15 µg/ml which will increase the heart rate by more than 10 beats per minute or systolic blood pressure by more than 15 mmHg.  
• All patients receiving LAA in doses sufficient to cause LAST should have oxygen applied, standard monitoring and intravenous access applied, and monitoring should continue for at least 30 minutes after completion of injection.

Management  
The management of LAST is clearly tabulated in the Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity. Management includes prompt airway management (to prevent hypoxia, hypercarbia and acidosis which potentiate LAST), lipid emulsion therapy, seizure control (with benzodiazepines and small doses of propofol if there is no cardiovascular compromise) and management of cardiac arrest (with adrenaline) and arrhythmias (with amiodarone).

New treatment recommendations include early administration of lipid emulsion. The reason for this is twofold: firstly, the shuttling effect of lipid emulsion is most effective early in the toxic event and secondly, adverse effects from lipid administration are mild and limited. The new treatment recommendations have also increased the maximum lipid dose to 12 ml/kg.

Mechanism of action of intralipid  
• Lipid “sink” theory, whereby lipid soluble LAAs are partitioned and removed from the body, is outdated. Rather the mechanism is:
  ◦ Shuttling effect: lipid emulsion acts as a dynamic carrier to scavenge LAAs away from high blood flow organs that are most sensitive to LAST (i.e. heart and brain) and redistribute it to organs that detoxify the drug (i.e. muscle and liver).
  ◦ Cardiotonic effect: lipid increases cardiac contractility which enhances shuttling effect. Lipid increases blood pressure via poorly understood effects on the peripheral vasculature.
  ◦ Postconditioning effect: the cellular effects of LAST may have overlap with cardiac ischaemia-reperfusion injury. Lipid activates cardioprotective pathways.

Novel local anaesthetic agents
Characteristics of an ideal local anaesthetic:
1. Short onset of action.
2. Specific nociceptive action.
3. Potent.
4. Less cardiotoxicity.
5. No local tissue toxicity.
6. Prolonged duration of action.

We have LAAs available to us which have the first three characteristics. Unfortunately, as far as local tissue toxicity and prolonged duration of action, we fall short. With the opioid epidemic in the developed world, having an effective non-opioid analgesic option with a prolonged duration would be welcomed. Currently, the only way to prolong duration is with adjuvants, catheters, repeated single-shot injections and new formulations. There has also been some work done into quaternary lignocaine derivatives such as QX-314.

Liposomal bupivacaine (exparel™)  
Pharmacology
• Liposomal bupivacaine is a prolonged-release formulation of bupivacaine indicated for single-dose administration.
• It consists of microscopic, spherical, multivesicular liposomes (DepoFoam drug delivery technology) containing encapsulated bupivacaine.
• The structure of liposome bupivacaine allows for drug release over 1 to 30 days.
• Liposomal bupivacaine has been shown to decrease toxic dosages in vivo. The sole fraction of bupivacaine available to enter the central nervous and cardiovascular systems is the free (non-liposomal) formulation.

Current clinical use
• Wound infiltration for bunionectomies and haemorrhoidectomies (Food and Drug Administration (FDA) approved 2011).
• Local surgical infiltration (FDA approved 2015).
• Interscalene brachial plexus block (FDA approved 2018).
• Maximum approved dose (adults) 266 mg.
• It is recommended to administer plain bupivacaine in a dose of less than 50% of the liposomal bupivacaine initially to help with early analgesia. However, other LAAs must not be mixed or given in the same site as this may cause a rapid release of free bupivacaine. Liposomal bupivacaine can be administered 20 minutes after lignocaine and other formulations of bupivacaine must not be administered 96 hours after administration of liposomal bupivacaine.8

• Neuraxial use: Only two phase-1 trials investigating epidural use. Prolonged sensory block, less motor block.

• Inadvertent intravenous (IV) injection and toxicity
  ◦ Low free bupivacaine exposure.
  ◦ 50% remains as intact exparel particles, 45% associated with lipid fragments and 5% free bupivacaine.
  ◦ Free bupivacaine releases slowly from liposomes after IV injection.

Limitations
• Cost is huge. Not available in South Africa.
• How do you manage early analgesia? We require more studies examining mixing with other LAAs.
• Difficult to re-administer.
• Neurotoxicity caused by the liposome metabolite compounds is unknown and the incidence of myotoxicity is higher.9

Conclusions
• Possible revolution in acute and chronic pain management.
• More trials required.
• Dose-ranging studies needed.
• Will catheters be replaced?

Other new formulations8

HTX-011
• Slow release bupivacaine in combination with a low fixed dose meloxicam.
• Both drugs are encapsulated in a bio-erodible polymer which undergoes slow and controlled hydrolysis and releases bupivacaine over 72 hours.
• Two phase-3 trials have been concluded (local infiltration for bunionection and open unilateral herniorrhaphy).

Neosaxitoxin
• Neurotoxin derivative found in shellfish.
• It has a higher affinity for Na+ channels Nav 1.7 and Nav 1.8 found in peripheral nerves as opposed to Nav 1.5 which is found in the myocardium.
• Theoretically may make neosaxitoxin safer.
• Fivefold longer duration of action.
• In high doses can cause facial paralysis and respiratory compromise

SABER-bupivacaine
• Sucrose acetate isobutyrate extended-release bupivacaine.
• Only for local infiltration. The structure also consists of benzyl alcohol and therefore cannot be used perineurally.

Intra-articular LAAs
LAAs such as bupivacaine, lignocaine and ropivacaine are chondrotoxic to human cartilage, although ropivacaine is less so. This came to light after the incidence of post arthroscopic glenohumeral chondrolysis (PAGCL) was reported in 2004. The toxicity seems to be related to duration of exposure as well as concentration of LAA.10 In addition, osteoarthritic cartilage seems to be more vulnerable compared to intact cartilage.11

LIA and WALANT

LIA12
Local infiltration anaesthesia (LIA) has mainly been employed for lower extremity joint replacement surgery. It involves injection of LAA, nonsteroidal anti-inflammatory and adrenaline. There have been a multitude of studies, all with differing results. The difficulty seems to be lack of standardisation and international accepted definitions which make the evaluation and comparison between studies difficult. This applies to the technique of LIA, multimodal analgesic techniques, fast-tracking and enhanced recovery protocols. The issue regarding chondrolysis with intra-articular infusions of LAAs does not apply for joint arthroplasty because all the cartilage is removed. The technique is very popular among orthopaedic surgeons even though hard evidence is lacking.12

WALANT13
The wide-awake local anaesthesia no tourniquet (WALANT) technique has been employed for hand surgery (e.g. carpal tunnel release, flexor tendon repair, tendon transfer, Dupuytren’s contracture and trapeziectomy). It involves the injection of LAAs with adrenaline. Its proponents believe that the avoidance of adrenaline in hand surgery is unjustified. Vasoconstriction occurs as a result of the adrenaline and therefore the tourniquet can be avoided which increases the comfort of the patient. The convenience of the surgical process is increased and adverse reactions such as nausea and vomiting are decreased. In addition, the patient maintains full motor control of his hand.

IV Lignocaine
It has been proposed that IV lignocaine has analgesic, anti-inflammatory, opiate-sparing, gut motility enhancing, antimicrobial and anti-tumoral effects.

Analgesic and antihyperalgaesic properties14
IV lignocaine does reduce pain intensity but also prevents hypersensitisation and has an antihyperalgaesic effect. The lignocaine should ideally be administered prior to surgical incision.
The mechanism of action is poorly understood but could be besides the Na⁺ channel blockade, blockade of the glycineensitive system, K⁺, Ca²⁺ channels, Gαq-coupled protein receptors and NMDA receptors. In addition, serotonin receptors and opiate receptors may be involved directly.

**Anti-inflammatory effects**

The anti-inflammatory effect of lignocaine is well documented. The amide LAAs inhibit leukocyte activation, migration and adhesion to the site of injury. Lignocaine blocks the priming of neutrophils and inhibits the release of superoxide anions and interleukin-1B. In animal models, lignocaine reduces leucocyte-endothelial cell adhesion and endothelial fluid leakage. It also inhibits TNFα signalling pathways that regulate angiogenic factors and vascular permeability.

**Effects on the respiratory system**

Lignocaine is a very weak respiratory depressant. 1.5 mg/kg decreases tidal volume and respiratory rate. The peak effect occurs 2.5–3 minutes after injection. In vitro, lignocaine also relaxes tracheal smooth muscle and can reverse muscular contraction induced by acetylcholine and histamine. Lignocaine 1–2 mg/kg is effective in laryngospasm prevention. Lignocaine can also blunt the cerebral haemodynamic effects of intubation.

**Cardiovascular effect**

Lignocaine is a class 1B antiarrhythmic according to the Vaughan Williams classification.

**Effects on the digestive tract**

Lignocaine helps prevent postoperative ileus. The exact mechanism seems multi-factorial and is not yet fully understood.

**Antithrombotic effect**

LAAs significantly inhibit platelet aggregation. A neuraxial block using LAAs is able to reduce the incidence of venous thrombosis by almost 50%.

**Antimicrobial properties**

This has been demonstrated in vitro. The addition of lignocaine to propofol may prevent syringe contamination. Lignocaine also has a direct antiviral effect against herpes simplex virus type 1.

**Antitumoural properties**

Direct and indirect tumoural effects of lignocaine have been demonstrated in vitro.

**Lignocaine and the auditory system**

Lignocaine has been studied as a tinnitus-suppressing agent. Unfortunately, systemic toxicity limits the practicality of using lignocaine as an effective treatment. Trans tympanic injection, intradermal injection and oral routes have been tried but without much success.

Research suggests that lignocaine suppresses some forms of tinnitus in either the cochlear, the central auditory system or perhaps both locations.

**Summary and clinical applications**

- Preventing propofol injection pain
  - Mechanism is unclear.
  - Lignocaine can be mixed with the propofol or pretreatment can be done with or without venous occlusion, low dose (< 20 mg) or high dose (> 20 mg).
  - Low dose lignocaine without venous occlusion seems to be the least effective.

- Improving postoperative recovery
  - Abdominal surgery: benefits include reduced pain, nausea, duration ileus, length of stay.
  - Breast surgery: possibly decreased chronic pain.
  - Spine surgery and arthroplasty: no evidence.
  - Thyroid surgery: reduction in opiate consumption and can reduce chronic pain.
  - Tonsillectomy: no evidence.
  - Cardiac surgery: no evidence.

**Dosing and duration**

Intravenous lignocaine dosage and duration are largely unknown. It should be administered prior to skin incision and possibly prior to induction. The most common bolus dose is 1.5 mg/kg the maintenance dose varies 1–5 mg/kg/hour the duration varies from the end of the surgical procedure to return of bowel function postoperatively. Personally, I would err on the lower dose for maintenance to prevent toxicity especially in a patient at risk. As far as duration is concerned, it is dependent on your setting and if a continuous infusion can be safely administered.

**Conclusion**

LAAs are one of the most commonly used drugs in anaesthesia. In addition, they can be used in a multitude of different administrations and for a multitude of reasons. For these reasons, it is important for anaesthetists and indeed, most practising doctors, irrespective of their specialty, to be well versed in their use.

**Conflict of interest**

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**ORCID**

C Quan [https://orcid.org/0000-0003-1039-4819](https://orcid.org/0000-0003-1039-4819)
References
1. Dippenaar JM. Local anaesthetic agents. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 1st ed. Centurion: Medpharm Publications; 2012. p. 331-58.
2. McLeod I. Local anaesthetics [Internet]. Medscape. 2019 [cited 2020 Sep 14]. Available from: https://emedicine.medscape.com/article/873879-overview.
3. El-Boghdady K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018;11:35-44. https://doi.org/10.2147/LRA.515412
4. Milner A, Welch E. Applied pharmacology in anaesthesiology and critical care. Centurion: Medpharm; 2012.
5. Neal J, Barrington M, Fettiplace M, et al. The third American Society of Regional Anesthesia and Pain Medicine practice advisory on local anesthetic systemic toxicity. Reg Anesth Pain Med. 2018;43:113-23. https://doi.org/10.1097/AAP.0000000000000720
6. Stephan S. Is postoperative pain relief really better after regional nerve blocks compared to general anaesthesia? SASA Congress 2020; 2020 Mar 15; CSIR Convention Centre, Pretoria.
7. Malik O, Kaye A, Urman R. Emerging roles of liposomal bupivacaine in anesthesia practice. J Anaesthesiol Clin Pharmacol. 2017;33:151-6.
8. Coppens S, Zawodny Z, Dewinter G, et al. In search of the Holy Grail: poisons and extended release local anesthetics. Best Pract Res Clin Anaesthesiol. 2019;33:212. https://doi.org/10.1016/j.bpa.2019.03.002
9. Prabhakar A, Ward C, Watson M, et al. Liposomal bupivacaine and novel local anesthetic formulations. Best Pract Res Clin Anaesthesiol. 2019;33:425-32. https://doi.org/10.1016/j.bpa.2019.07.012
10. Piper S, Kramer J, Kim H, Feeley B. Effects of local anesthetics on articular cartilage. Am J Sports Med. 2011;20:1-9. https://doi.org/10.1177/0363546511402780
11. 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. https://doi.org/10.1213/ANE.0b013e31829481ed
12. Rawal N. Local infiltration analgesia and other multicomponent techniques to improve postoperative outcome - are we comparing oranges and apples. Reg Anesth Pain Med. 2011;36:417-20. https://doi.org/10.1097/AAP.0b013e3182286295
13. Al Youha S, Lalonde DM. Update/review: Changing of use of local anesthesia in the hand. Plast Reconstr Surg Glob Open. 2014;2: e150. https://doi.org/10.1097/GOX.0000000000000095
14. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadel L. Perioperative use of intravenous lidocaine. Drugs. 2018;78:1229-46. https://doi.org/10.1007/s40265-018-0955-x