Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic exploration report number:	TER314
Topic:	Neuropad for screening and detection of early signs of diabetic peripheral neuropathy (DPN).
Summary of findings:	In 2018, National Institute for Health and Care Excellence (NICE) Medical Technologies Guidance [MTG38] concluded that there was insufficient evidence to support the use of Neuropad in patients in whom 10g monofilament testing for DPN is not possible. Their recommendations also stated that cost modelling was uncertain because of the limited clinical-effectiveness evidence at the time. This Guidance is being updated. This topic exploration report identified two primary studies and one economic study published since 2018. The economic study analysed the cost-effectiveness of Neuropad for detecting early signs of DPN, either as a complement to the reference standard or as a substitute. Both primary studies concluded that Neuropad demonstrates high sensitivity, although the reference standards used did vary. One study found Neuropad to demonstrate higher sensitivity when compared to the 10g monofilament application. Another study found that the visual indicator plaster method (IPM) (including Neuropad) demonstrated higher sensitivity when compared to the neuropathy disability score (NDS) and vibration perception threshold (VPT). One study reported that Neuropad demonstrated moderate specificity, whereas another study found the IPM (including Neuropad) demonstrated low specificity. A recent cost-effectiveness analysis found that Neuropad, in combination with the 10g monofilament application (adding Neuropad to the pathway) has the potential to be cost-effective and is the dominant strategy in their analysis.

Introduction and aims

DPN is one of the most common complications of both type one and type two diabetes (Zografou et al. 2020). DPN is often referred to as diabetic foot disease and can lead to the development of hard-to-treat foot ulcers, lower limb amputations and even an early death.

Neuropad is a simple, painless, and non-invasive screening device for use in people with diabetes which could be performed by the patients themselves or in-clinic. The device detects sudomotor dysfunction (inadequate sweat production), which may indicate that a person is in the early stages of developing DPN (NICE 2018). It contains the blue complex salt anhydrous cobalt II chloride, which in the presence of water (sweat) absorbs six water molecules and its colour changes from blue to pink.

Health Technology Wales researchers searched for evidence on the use of Neuropad, also known as visual indicator tests, for signs of DPN.

The National Institute for Health and Care Excellence (NICE) produced Medical technologies guidance [MTG38] in September 2018, which included recommendations on Neuropad for detecting preclinical DPN and was informed by a review of the available evidence. Thus, we searched for evidence on the clinical effectiveness of Neuropad from 2018 onwards.

Evidence overview

Overview

We identified relevant Medical Technologies Guidance from NICE in 2018. We also identified one systematic review (Fernández-Torres et al. 2020) published after this guidance. However, this does not include any additional published evidence about Neuropad since NICE's evidence review. We did identify two primary studies, Zografou et al. (2020) and Panagoulias et al. (2020) and one cost-effective analysis (Rodriguez-Sanchez et al. 2020) published since NICE's evidence review that contribute new findings.

We identified one primary study which aimed to evaluate Neuropad's diagnostic accuracy in detecting DPN in patients with diabetes when compared to other devices including the Michigan neuropathy screening instrument questionnaire (MNSIQ) and examination (MNSIE), the 10g monofilament application and the Biothesiometer measurement (BIO) (Zografou et al. 2020). We identified a second primary study which aimed to determine the effectiveness of dryness of foot skin measured using Neuropad as a predictor of DPN risk, compared to the NDS and VPT.

Guidance

NICE recommendations stated that the case for adopting Neuropad to detect preclinical DPN was not supported by the evidence (NICE 2018). In their evidence based recommendations, there was insufficient evidence to support the use of Neuropad in patients in whom the 10g monofilament testing for DPN is not possible (NICE 2018). In September 2021, NICE started a review of this guidance.

Diagnostic accuracy

The evidence identified by NICE comprised 18 studies, of which 13 were full text articles and five were abstracts. Of the 18 studies, 17 investigated the diagnostic accuracy of Neuropad against a reference standard and 1 reported its ability to predict the risk of diabetic foot ulceration. The most common reference standard used was the NDS. All the studies were prospective observational, cross-sectional, or longitudinal cohort studies. Meta-analysis carried out by the external assessment

centre showed that Neuropad had a sensitivity of 89.4% (95% confidence interval [CI] 83.2 to 93.5) and a specificity of 60.3% (95% CI 50.9 to 69), when using a neuropathy disability score of five or more as a reference standard for the diagnosis of DPN. Using a NDS of five or more identifies patients with moderate to severe neuropathy. Based on this, the committee concluded that Neuropad demonstrated good sensitivity but poorer specificity in comparison as a diagnostic test for DPN.

Zografou et al. (2020) compared Neuropad's sensitivity and specificity in diagnosing DPN to MNSIQ, MNSIE, BIO, and the 10g monofilament application (n = 174). It is not clear from this study how a final DPN diagnosis was determined or what reference standard method was used to do this. Sensitivity of Neuropad testing was 95% versus the 10g monofilament application, 73% versus BIO, 73% versus MNSIE and 75% versus MNSIQ. Corresponding specificities were 69, 81, 90 and 92%, respectively (Zografou et al. 2020).

Similarly, Panagoulias et al. (2020) (n = 308) also found that IPM testing showed higher sensitivity (86%) when compared to the NDS and VPT which was reported at 40% and 39% respectively. The IPM showed lower specificity (49%) than what was reported for NDS and VPT which were 87% and 89% respectively (Panagoulias et al. 2020).

Safety and Clinical Outcomes

Neither (Fernández-Torres et al. 2020), Zografou et al. (2020) or Rodriguez-Sanchez et al. (2020) reported any safety concerns. However NICE (2018) stated that if Neuropad were to be introduced into the community, clear guidance on its use would be needed to avoid misleading results.

Economic evidence

In their economic analysis, NICE (2018), Rodriguez-Sanchez et al. (2020) concluded that Neuropad testing alone would be cost incurring: using Neuropad instead of the 10g monofilament application testing would likely increase costs because Neuropad has a lower specificity for detecting DPN. Their advice stated that the cost modelling for this technology was uncertain because of the limited clinical-effectiveness evidence available (NICE 2018).

Rodriguez-Sanchez et al. (2020) carried out a cost-effectiveness analysis using a Markov model which assessed the costs and outcomes of using Neuropad as a test for diabetic neuropathy in addition to the 10g monofilament application or as a replacement for the 10g monofilament application. They found using Neuropad in addition to the 10g monofilament application to lead to higher health gains and lower costs, i.e., this was the dominant strategy.

Areas of uncertainty

We identified evidence comparing Neuropad to several other tests that can be used to screen for or diagnose early DPN. In any more detailed appraisal, consideration would be needed as to what to use as a reference standard, and whether Neuropad replaces existing tests or is used in addition to them.

Clinical experts from the NICE guideline as of 2018 advised that a positive Neuropad test alone would currently not lead to a change in management, because it would not alter the definition of risk status in a patient with diabetes. A patient diagnosed with preclinical DPN using Neuropad testing could be offered more attentive foot care, but it is unclear to what extent this would lead to beneficial clinical consequences.

Literature search results

Health Technology Assessments and Guidance
NICE. (2018). Neuropad for detecting preclinical diabetic peripheral neuropathy. Medical technologies guidance [MTG38] Published: 10 September 2018. The National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/mtg38 [Accessed 19 Oct 2021].
Evidence reviews and economic evaluations
Rodriguez-Sanchez B, Pena-Longobardo LM, Sinclair AJ. (2020). Cost-effectiveness analysis of the Neuropad device as a screening tool for early diabetic peripheral neuropathy. The European journal of health economics : HEPAC : health economics in prevention and care. 21(3): 335-49. doi: https://dx.doi.org/10.1007/s10198-019-01134-2
Individual studies
Panagoulias GS, Eleftheriadou I, Papanas N, et al. (2020). Dryness of Foot Skin Assessed by the Visual Indicator Test and Risk of Diabetic Foot Ulceration: A Prospective Observational Study. Frontiers in endocrinology. 11: 625. doi: https://dx.doi.org/10.3389/fendo.2020.00625 Zografou I, Iliadis F, Sambanis C, et al. (2020). Validation of Neuropad in the Assessment of Peripheral Diabetic Neuropathy in Patients with Diabetes Mellitus Versus the Michigan Neuropathy Screening Instrument, 10g Monofilament Application and Biothesiometer Measurement. Current vascular pharmacology. 18(5): 517-22. doi: https://dx.doi.org/10.2174/1570161117666190723155324
Ongoing research
No relevant evidence identified.
Evidence submitted by topic proposer
Fernández-Torres R, Ruiz-Muñoz M, Pérez-Panero AJ, et al. (2020). Instruments of Choice for Assessmentand Monitoring Diabetic Foot: A Systematic Review. J Clin Med. 9(2). https://doi.org/10.3390/jcm9020602 *We have included this recent systematic review for completeness, but it does not include any evidence on Neuropad additional to that summarised by NICE as part of MTG38.*

Date of search:	October 2021
Concepts used:	"Neuropad" OR "visual indicator test" OR "diabetic peripheral neuropathy"