Pragmatic Opioid Use in Painful Diabetic Neuropathy

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The management of painful diabetic neuropathy poses a tough clinical challenge. Although opioid analgesics are considered as second- or third-line agents in the management of moderate-to-severe neuropathic pain, prescription of opioids for this indication is higher than expected. This narrative review is a recommendation on how to ensure pragmatic use of opioids for those with painful diabetic neuropathy while avoiding complications such as opioid overdose, opioid diversion and the development of opioid-use disorder. Risk mitigation strategies at the level of the clinician include periodic assessment and documentation of clinical details, treatment history and psychosocial status. Using a multimodal approach to pain management, medication counselling, adherence monitoring programmes, evidence-based opioid dosing strategies and empowering patients to make treatment decisions are effective strategies in reducing risk associated with prolonged opioid use. At the organisational and policy level, using prescription drug monitoring programmes, evidence-based opioid dosing strategies and empowering patients to make treatment decisions are effective strategies in reducing risk associated with prolonged opioid use. At the organisational and policy level, using prescription drug monitoring programmes, evidence-based opioid dosing strategies and empowering patients to make treatment decisions are effective strategies in reducing risk associated with prolonged opioid use. At the organisational and policy level, using prescription drug monitoring programmes, evidence-based opioid dosing strategies and empowering patients to make treatment decisions are effective strategies in reducing risk associated with prolonged opioid use.

The prevalence of diabetes in the worldwide adult population has increased from 4.7% to 8.5% since 1980.1 Peripheral neuropathy is found in 30–90% of patients with diabetes mellitus, and 16–34% of diabetes patients suffer from painful diabetic neuropathy (PDN).2,3 South Asians are particularly prone to this complication which leads to decreased quality of life and increased healthcare costs.4 The symptomatic management of PDN with a single treatment approach remains a challenge.5 The current guidelines recommend different medications as first- and second-line agents.6 A review of recent recommendations described tricyclic agents (e.g., amitriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine), and gabapentinoids (e.g., pregabalin, gabapentin) as the first-line agents for symptomatic management of PDN.7 Opioid analgesics (e.g., morphine, methadone, tapentadol, tramadol) are recommended as second- or third-line agents and their use is recommended for management of moderate-to-severe neuropathic pain.8,9 Despite the recommendations, use of opioids for the management of PDN commonly precedes that of other drugs.10 This is a narrative review that aims to provide an overview of the existing evidence on pragmatic use of opioids for those suffering from PDN while avoiding complications associated with opioid use such as overdose, diversion and development of opioid-use disorder.

Morphine and methadone are high-potency, full mu-opioid agonists that effectively manage moderate-to-severe pain. A meta-analysis on the efficacy of morphine for neuropathic pain management demonstrated equivocal efficacy of the drug (numbers needed to treat = 3.7; range 2.6–6.5) with a maximum daily dose of 90–180 mg/day.11 A meta-analysis of efficacy of methadone use for neuropathic pain management showed similar results, with the daily dose ranging between 10–80 mg/day.12 Long-term use of these potent mu-opioid agonists for chronic non-cancer pain is associated with an increased risk of opioid-use disorder, overdose events, fractures, myocardial infarctions and endocrinological harm.13 Opioid-use disorder is defined as a ‘problematic pattern of opioid use leading to clinically significant impairment or distress’ 13

Tramadol is a low-potency, centrally acting, weak mu-opioid agonist with aminergic activity that is used to manage PDN.14 It carries a risk of serotonin syndrome, especially when tricyclics are used concomitantly or doses higher than 400 mg/day are consumed.14 Another risk with chronic tramadol use is that it lowers seizure threshold, even at low doses.14 Development of opioid-use disorder with use of tramadol is likely to be lower. Low-dose opioid use is defined as ≤40 mg morphine or equivalent per day.15 The usual starting dose of tramadol (50–100 mg), is equivalent to 7.5–15.0 mg of morphine.15 Thus, the risk of opioid-use disorder with tramadol is expected to be low.14 However, opioid-use disorder due to tramadol has been reported.16 Tapentadol is a relatively new, centrally acting, weak mu-opioid receptor agonist and norepinephrine and serotonin receptor antagonist that is commonly prescribed for management of PDN.17

Keywords
Diabetes, neuropathy, opioids, analgesia, opioid abuse, opioid addiction

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Along with pregabalin and duloxetine, it is the only drug approved by the US Food and Drug Administration for PDN management in an oral dose range of 50–700 mg per day. Despite claims of low abuse potential, it has been found to be associated with opioid-use disorder in post-marketing evaluations.\textsuperscript{10}

Besides the risk of development of opioid-use disorder, prolonged and/or excessive use of opioids is associated with risk of opioid overdose and other systemic complications. Hence, we offer pragmatic suggestions to ensure safe and effective use of opioid analgesics in the management of PDN. To begin with, we offer recommendations for risk mitigation that can be executed at the clinician level. In the end, we offer recommendations on risk-mitigation strategies at organisation and policy level.

### Risk mitigation strategies at the level of the clinician

#### Clinical review

The first step is a thorough clinical assessment of patients with PDN to ensure that the diagnosis is correct and comprehensive. Other metabolic, toxic and inflammatory causes of neuropathic pain such as vitamin B12 deficiency or hypothyroidism and restless leg syndrome, might be contributing to pain and should be ruled out.\textsuperscript{1} Detailed clinical assessment and documentation of the presenting complaints, such as pain (quality, intensity, diurnal pattern, accompanying complaints, etc.), general medical history and past history of medical, surgical history, and psychiatric disorders, are necessary. Documentation of family history, personal history, psychosocial history (for e.g. premorbid personality) and current physical and psychological status should be done. A periodic quantitative assessment and documentation of pain severity and quality of life is an important part of clinical review.\textsuperscript{2,12}

#### Drug history review

While considering opioid therapy for PDN, the healthcare provider should enquire about past or current history of substance-use disorder; prescription drug misuse, as well as details of past opioid prescriptions. A history of treatment non-adherence and aberrant drug use behaviours should also be taken. Table 1 enumerates the various factors that are associated with prescribed opioid misuse and could be considered as red flags when considering treatment with opioid analgesics or after having started opioids.\textsuperscript{12}

#### Treatment review

Opioid analgesics are only to be considered when multiple first-line agents (tricyclics, serotonin-norepinephrine reuptake inhibitors [SNRIs] and gabapentinoids) cannot control pain alone or in combination.\textsuperscript{1} Hence, ensuring adherence to treatment regimen using these agents is important before considering opioids. The time and dose of administration should be checked and attuned to the diurnal variation in symptoms. For example, administer duloxetine or pregabalin 1–2 hours before expected onset of symptoms. The next step is to ensure that these drugs have been used in maximally tolerated doses before using opioids as an adjunct medicine. Try interchanging drugs (from duloxetine to pregabalin, or vice versa) or augmentation strategies (from monotherapy to combination therapy).\textsuperscript{2}

A multimodal, multidisciplinary approach to pain management needs to be employed during management of PDN. Non-pharmacological therapy for PDN such as physiotherapy, psychological therapies (e.g., cognitive behavioural therapy, pain-coping skills training, mindfulness-based interventions) and interventional procedures must be considered.\textsuperscript{11} Referring the patient to a pain specialist for more holistic management is a good strategy.\textsuperscript{12}

#### Using screening tools for risk stratification of patients

These tools, in conjunction with clinical assessment, could lead to more accurate risk prediction of outcomes such as opioid misuse and opioid-use disorder. The Opioid Risk Tool is one such validated tool.\textsuperscript{15} The revised Screener and Opioid Assessment for Patients with Pain is also used to predict subsequent aberrant drug use behaviors.\textsuperscript{16} Available literature on these screening tools is on diagnostic accuracy, but evidence on effectiveness of these tools in predicting outcomes related to opioid-use disorder is insufficient. These tools can be pre-emptively used to identify patients who would need a greater degree of clinical supervision.

#### Medication counselling

Effective patient education and counselling maximises patient involvement in treatment. A decision to start opioid analogesics should be the result of shared decision-making by the patient and physician.\textsuperscript{30,11} It should be considered after exhausting other treatment options. At the same time, certain patients might be wary of starting opioids, despite inadequate pain management on other treatment.\textsuperscript{15} So a realistic cost–benefit analysis of starting opioid analogesics for PDN must be done and results discussed with patients and caregivers. Inform them about treatment goals, and possible adverse effects like constipation, nausea, vomiting, pruritis, myoclonus, drowsiness, risk of fall, endocrinological disturbances and cognitive dysfunction. The risk of opioid-use disorder, overdose, and need to avoid co-administration with alcohol and benzodiazepines must be clear to the patient.

#### Pain medicine agreements and urine drug testing

These agreements are essentially patient–clinician treatment contracts that enlist the risks and benefits to be expected from opioid use, an undertaking not to alter prescription, exceed prescribed daily dose, overshoot prescribed duration of therapy, or share one’s medication supply with others. Usually, these agreements also stipulate periodic urine drug testing to detect opioid-use disorder or diversion and for adherence monitoring.\textsuperscript{23} There is fair, but limited, evidence supporting the use of pain medicine agreements and urine drug testing for high-risk patients on chronic opioid therapy.\textsuperscript{24} In light of insufficient evidence regarding their effectiveness and ethical concerns over their use, further research is needed to get more clarity on the objectives, active elements, and justifications for using these strategies.\textsuperscript{24} The agreements need to be more patient centric.\textsuperscript{28}
Drug prescription
The PDN symptomatology may exhibit a highly variable course. Opioids should be prescribed in a minimum required dose for symptom relief. Although there are no significant differences between long- and short-acting opioids on effectiveness and adverse effect outcomes, short-acting opioids at the lowest possible dose should be preferred.10,15 If painful symptoms exacerbate at night or in the case of breakthrough pain, short-acting preparations should be preferred for emergency dosing.24 Prescriptions should be for a finite period of time, and automatic refills should not be allowed. If a long-acting opioid is prescribed, dose titration needs to be done cautiously since the drug accumulates, leading to adverse events. Since the underlying theme of opioid-dosing recommendations is to prescribe the lowest possible dose, patients should be empowered, and encouraged, to down-titrate doses when their health permits. The use of scored tablets helps in facilitating patient-centric down-titration of doses.26 Symptomatic worsening may be mitigated by initiating or intensifying treatment with other neurotropic drugs, approved for use in PDN.

Opioid dosing strategies
There is insufficient evidence to refute or support use of scheduled continuous dosing versus as-needed dosing. Studies have shown that time-scheduled dosing is associated with higher overall opioid dosage as compared with as-needed dosing, but a review of the evidence indicates that there is no discernible difference between the two in terms of pain and quality-of-life outcomes.23,24 On the issue of opioid rotation versus maintenance of current therapy, the recommendation is that the decision to undergo opioid rotation needs to be taken in the context of low probability of a successful outcome, co-morbidities, concomitant pharmacotherapy and logistics.25 As far as the tapering protocols are concerned, the Centers for Disease Control and Prevention (CDC) recommends tapering off opioids weekly at a rate of 10–50% of the original dosage, but this should be individualised.26

Using alternative drug formulations
Tramadol, tapentadol and morphine are available as extended-release and long-acting (ER/LA) preparations. In theory, using them would help avoid the sudden spike in opioid levels, thereby reducing the abuse potential of analgesics. However, currently there is insufficient evidence to support use of ER/LA preparations to improve outcomes related to opioid-use disorder. Prescription of ER/LA preparations could be associated with an increased risk of opioid-use disorder and overdose, as per a large cohort study.27 The American Society of Interventional Pain Physicians recommends short-acting preparations at the lowest possible dose for management of chronic non-cancer pain.28

Use of deterrent or tamper-resistant formulations is a novel pharmaceutical strategy to prevent individuals from resorting to crushing or dissolving pills and then snorting or injecting them for increased bioavailability. Development of such formulations is in nascent stage and evidence supporting the benefit in mitigating opioid-use disorder is insufficient.29 A recent randomised controlled trial indicated that transdermal buprenorphine could be a useful agent in PDN, if common adverse effects such as nausea and vomiting are managed effectively.30

Periodic screening and follow-up
Patients with PDN on opioid therapy should be screened regularly for emergence of opioid-use disorder. Regular screening for psychiatric conditions such as depression and anxiety may also be indicated. Validated tools to screen for opioid-use disorder are available. The

| Table 2: Opioid-use disorder diagnostic criteria (based on American Psychiatric Association’s Diagnostic and Statistical Manual-5) |
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| Opioid-use disorder is diagnosed if two or more of the following criteria are present in a person taking opioids in a 12-month period:* |
| • opioids are often taken in larger amounts or for a longer period than was intended; |
| • there is a persistent desire or unsuccessful efforts to cut down or control opioid use; |
| • a great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects; |
| • craving, or a strong desire or urge to use opioids; |
| • recurrent opioid use resulting in a failure to fulfil major role obligations at work, school, or home; |
| • continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids; |
| • important social, occupational or recreational activities are given up or reduced because of opioid use; |
| • recurrent opioid use in situations in which it is physically hazardous; |
| • continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused, or exacerbated by the substance; |
| • exhibits tolerance;** or |
| • exhibits opioid withdrawal.† |

*Patients who are prescribed opioid medications for analgesia may exhibit withdrawal and tolerance, but would not necessarily be considered to have a substance-use disorder.12

**Tolerance is defined as: 1) a need for markedly increased amounts of opioids to achieve intoxication or desired effect, or 2) a markedly diminished effect with continued use of the same amount of an opioid.12

†Opioid withdrawal is defined as three (or more) of the following, developing within minutes to several days after cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer), or administration of an opioid antagonist after a period of opioid use: dystrophic mood, nausea or vomiting, muscle aches, lachrimation or rhinorrhea, pupillary dilation, piloerection, sweating, diarrhoea, yawning, fever, or insomnia.28

Current Opioid Misuse Measure is a 17-item questionnaire developed and validated to identify those patients who are currently misusing their prescribed opioid medication.29 The Addiction Behavior Checklist is a 20-item instrument which can identify problematic behaviour associated with long-term opioid use in patients with chronic pain.30 Individualised treatment that is periodically reassessed, using urine drug testing, pill counts, or other measures if needed, should form part of follow-up visits. The CDC recommends that clinicians should frequently reassess patients for pain and quality-of-life outcomes, and adverse events in the first month after initiating opioids for non-malignant pain.31 The subsequent follow-up rate could be tailored to the patient’s needs and should occur within a 1–4 week range.

Stakeholder involvement
Opioid-use disorder is defined as ‘a problematic pattern of opioid use leading to clinically significant impairment or distress’.12 Table 2 lists the diagnostic criteria of opioid-use disorder as per the American Psychiatric Association’s Diagnostic and Statistical Manual-5.12 Opioid-use disorder exists on a continuum of severity; meeting more than one of the criteria of opioid-use disorder could have serious treatment implications. All members of the diabetes care team and patients’ caregivers, must be aware of the symptoms and signs of opioid-use disorder. This may help in early recognition and limitation of this disorder. An individual taking prescribed opioids under medical supervision might exhibit some of these criteria, such as tolerance and withdrawal, but that would not necessarily mean that they have opioid-use disorder. Educational and training sessions should be provided to patients and caregivers on the safe use of opioids, disposal of expired medications and safe storage of opioids.32
Table 3: Pragmatic suggestions to limit opioid-use disorder in persons with diabetic painful neuropathy

| Pre-description | With prescription | Post-prescription |
|-----------------|------------------|------------------|

**Clinical review:** rule out other treatable causes of pain, relevant clinical details

- Medication counselling: expected benefits, side effects, limitations
- Adherence monitoring: urine drug testing, pill counts, frequent follow-up, risk monitoring with tools

**Pharmacological review:** review drug history

- Drug prescription: low-dose opioids, short-acting for shortest possible duration
- Empower and inform patient to make treatment decisions

**Treatment review:** record treatment rationale, process and outcomes

- Plan non-pharmacological management: cognitive behavioural therapy, pain-coping skills training, mindfulness-based behaviour
- All-round stakeholder involvement for timely identification of problematic behaviour

**Risk stratification:** assess risk of opioid-use disorder

- Table 3: Pragmatic suggestions to limit opioid-use disorder

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**Conclusion**

The epidemic of diabetes shows no sign of abating. It may be expected, therefore, that prescription opioids for PDN among people with diabetes mellitus will continue to increase. The pragmatic suggestions shared in this narrative review should help limit the potential adverse consequences associated with prolonged opioid use among those using these medicines for PDN. The principles described here are relevant not only to PDN care, but to the management of other chronic painful conditions as well as that require prescription of opioid analgesics.