Treatment of Postherpetic Neuralgia

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Postherpetic neuralgia (PHN) remains one of the most troublesome common chronic neuropathic pain conditions. Many controlled trials have been published showing good efficacy and reasonable tolerability. These include gabapentinoids, opioids, tricyclic antidepressants, and topical lidocaine and capsaicin. Combination therapies are possible, but have not been proven, and long-term follow-up is limited. Only few case series exist for surgical and other invasive therapies and their role remains uncertain.

Introduction

Postherpetic neuralgia (PHN) is a painful aftermath of herpes zoster, an acute inflammation of spinal nerves due to reactivation of varicella zoster virus residing dormant in sensory ganglia. Once rash, the hallmark sign of herpes zoster has healed, pain gradually improves. Protracted pain, originating in the virus-affected somatosensory pathways, is referred to as PHN and is characterized by burning, smarting and lancinating pain, sensory impairment, and mechanical allodynia in the affected dermatome [1]. There is no consensus on the time point at which acute herpetic pain is considered to have developed into PHN and definitions range from the time immediately to 6 months after the healing of the rash [2]. A strict time-based definition may be advantageous in the comparison of various clinical trials, but is unlikely to be a good measure of pathophysiologic changes. The few histopathologic and neurophysiologic studies that have been carried out from the early stages of herpes zoster do not suggest a strong correlation between recovery of pain and neural damage, and there are conflicting data as to how long after the original attack inflammatory changes are present [2]. Dworkin and Portenoy [3] have suggested a three-stage classification into acute, subacute, and postherpetic neuralgias, with the latter to be diagnosed 120 days from rash onset. Most clinical trials on PHN have used a 3-month post-rash criterion for enrollment; however, in practice, most patients participating in these trials have had stable PHN lasting for several months or years, which is compatible with any definition.

Natural Course of the Disease

Most patients under the age of 50 years recover from acute herpes zoster without painful sequelae and in the few for whom PHN sets in, the long-term prognosis is likely to be good [4,5] The picture is somewhat different in the elderly, with 3% to 40% still reporting pain at 12 months, depending on the severity of pain and timeliness of antiviral therapy [4–6].

Clinicians treating patients with established PHN frequently are asked of the long-term prognosis of the pain. Lack of reliable data prevents any firm advice. In some cases, patients do well. In a study of 88 patients with protracted (≥ 1 year) pain assessed in a pain clinic, one third had mild pain and no disability when reassessed an average of 2 years later [7]. Helgason *et al.* [4] followed 13 patients with PHN of 12 months' duration for an average of 6 years; seven of them became pain-free between 2 and 7 years. Data are very limited regarding the long-term prognosis of chronic, disabling PHN, which is the most common form of the condition seen in pain clinics.

Risk Factors for Postherpetic Neuralgia

Several observational studies have consistently shown that age increases the likelihood of one contracting herpes zoster and increases the risk of prolonged pain, and ultimately chronic PHN. Most case series also suggest that intensity of pain independently of age increases the risk of PHN, at least during the first year [8•]. Other putative risk factors include presence of prodromal pain, severe rash, female sex, reduced vibratory sensitivity in feet (suggestive of generalized neuropathy), sensory change, paravertebral muscle electromyography abnormalities, inflammatory changes on magnetic resonance imaging, fever, diabetes, psychologic distress, and living alone. Most of these results come from single studies and have not been corroborated. There is no equation one can rely on in determining a prognosis in individual cases, but severe pain with a prodrome in an elderly patient suggests a major risk of protracted pain [8•].

Epidemiology

The prevalence of PHN in the general population is unknown. Indirect evidence from a community-based study based on general practitioner records suggests a lifetime prevalence for PHN (defined as pain at 1 month after the rash) of 0.7 (95% confidence interval [CI], 0.4–1.0) per 1000 population [9]. In another study in which 1071 elderly patients between the ages of 69 and 99 years were interviewed regarding their history of shingles and subsequent protracted pain; 39 (3.8%) of the responders reported PHN of at least 3 months duration [10]. Seventeen (1.7%) of the interviewees reported ongoing pain as an aftermath of shingles; 15 of them had pain for 6 months or longer. Unfortunately, the intensity of pain or associated disability was not estimated and none of these patients underwent clinical examination or had their medical records reviewed; however, almost all were reportedly seen by their general practitioner during their bout of acute shingles. The 15 patients led to an estimated prevalence of 14/1000 in this elderly population.

Pathophysiology of Postherpetic Neuralgia

Of the human neuropathic pain conditions, PHN has been considered as one of the most intriguing and fruitful for pathophysiologic study. It is known that following the initial viral replication in the ganglion, peripheral nerve, and nerve root, intense inflammatory changes also occur in the spinal cord and brain stem, both ipsilaterally and contralaterally [2]. The location, extent, and severity of subsequent neural damage and secondary changes common to every nerve lesion determine the complex pathophysiologic pattern that dictates the clinical manifestations in each individual case [11••]. There is compelling evidence from skin biopsies, subcutaneous and cutaneous drug challenges, and psychophysical measurements for C-fiber sensitization (to at least adrenaline, capsaicin, and heat) that the peripheral afferent may be a significant pain generator in a subset of patients with PHN. Similarly, major sensory loss, associated with mechanical allodynia, postmortem histopathology, and lack of responses to peripherally aimed treatments are suggestive of predominant central mechanisms in another subset [11••]. The primary peripheral and central pathophysiologies represent the ends of the spectrum, with most patients showing on examination evidence for several different neural mechanisms simultaneously [2]. A mixture of mechanisms explains why most therapies alone are of partial benefit only.

Prevention of Postherpetic Neuralgia

It generally is accepted that early treatment of acute herpes zoster reduces the mean duration of pain and reduces the number of patients with PHN at 3 and 6 months. Nevertheless, elderly patients with severe pain at onset still face a substantial risk of PHN despite appropriate treatment with antivirals. Oral prednisolone in conjunction with antivirals does not appear to prevent PHN [12]. An insufficiently powered study suggested that amitriptyline is superior to placebo in preventing PHN at 6 months [13]. However, antiviral treatment was not predetermined, but left to the individual general practitioner to decide. In the analysis, the outcome was crucially dependent on the unusually high percentage of patients on placebo and acyclovir (47%) at 6 months and much larger populations are needed for a more decisive result.

More than 30 years ago, Colding [14] was the first to suggest that nerve blockade during acute herpes zoster reduces the risk of development of PHN. Since then, a legion of studies have been published, followed by reviews by several authors [15–17]. Conclusions from these reviews vary somewhat, owing to variability in the original studies in design, methodology, and outcome measures. Most of the prevention studies are retrospective case series and randomized, controlled trials are rare [18–20]. Three prospective, randomized studies deserve a comment. Tenicela *et al.* [18] compared a series of sympathetic or epidural blocks with placebo in 20 patients with herpes zoster for less than 6 weeks. Non-responders were given a second series of open-label bupivacaine. There were no short-term or long-term differences between groups in pain. However, if dysesthesia not requiring treatment was included in the analysis, a difference was shown in favor of bupivacaine. In a much larger, properly powered, prospective study of 569 participants, prolonged epidural blockade with bupivacaine and prednisolone without concomitant antivirals was compared with intravenous acyclovir and prednisolone [19]. The patients were at high risk for PHN (entry criteria included a baseline pain level of ≥ 7/10 and an age of ≥ 55 years). In this resource-demanding study, far fewer patients in the epidural blockade group developed PHN than in the intravenous acyclovir group. The result from epidural blockade is impressive and the failure rate is substantially lower than in a similar open-label study with bupivacaine alone [21]. In another study, only published in abstract form, 583 patients, all taking antiviral medication, were randomized to receive a single-shot epidural injection with steroids and bupivacaine or no additional treatment. There were no differences in the percentage of PHN patients at 3 or 6 months [20].

No other treatment but early antiviral medication may be recommended for routine prevention of PHN. If the deadline of 72 hours from rash for commencement of antivirals is missed or if the patient is in very severe pain, the managing clinician cannot rely on any published guidelines. The studies mentioned previously give some support for the use of epidural blockade in these cases, both for improved control of pain and possible reduction of the risk of PHN. The question of whether noninvasive pain-control methods, including strong opioids and novel antiepileptic drugs, are similarly effective remains untested.

Table 1. Application of evidence-based treatments for postherpetic neuralgia

General	Specific	
Make note of prognosis 50% of postherpetic neuralgia patients of less than 6 months duration will be better in 6 months [4,7] Examine sensory profile* Severe sensory loss, minimal allodynia to punctuate and thermal stimuli, moderate to severe dynamic mechanical allodynia only (deafferentation, with complete loss of small fibers) [2,11••] Mostly preserved sensation, significant allodynia to all stimuli (including hear†), positive capsaicin, small fiber sensitization ("irritable nociceptor") [11••,24•] Assess sleep, quality of life, mood, and degree of disability Consider combinations of mechanistically distinct agents	Deafferentation type Pregabalin/gabapentin dose escalation to maximum tolerated; discontinue only if no effect or poor tolerability [32,33,34•,35] Add nortriptyline up to 150 mg/d, being cautious of side effects; discontinue only if no effect or poor tolerability; in mild cases, consider tramadol [25–29,46]†Add strong opioid and continue only if significant response from low doses [30••,31]‡Consider lidocaine patch if significant allodynia remains [36–39] Challenge assumed effectiveness by tapering individual medications For refractory cases, contemplate neuroablative surgery if severe physical and psychologic disability is present and cannot be helped by cognitive-behavioral means	Irritable nociceptor type Lidocaine patch or capsaicin [36–39,41,42] Add pregabalin/gabapentin [32–35] Add strong opioid or tramadol (in mild cases) [30,31,46] Add nortriptyline, but be cautious of major side effects [25–29]†Challenge assumed effectiveness For insufficient pain relief, consider spinal cord stimulation [53] For refractory cases, contemplate neuroablative surgery

*Many patients have both types of sensory change.
†Exercise caution when combining tramadol with a tricyclic.
‡Examples of low doses are 40 to 60 mg of oxycodone, 60 to 120 mg of morphine, or 15 to 20 mg of methadone.

Treatment of Postherpetic Neuralgia: Emphasis on Evidence Base

It generally is accepted that the first line of treatment of PHN is pharmacologic. Contrary to surgical and other non-drug therapies, there have been numerous good-quality controlled trials on the medical treatment of PHN since the early 1980s. These studies have provided the framework for this review. Different from other recent reviews [22,23], we mainly discuss results from good-quality pharmacologic controlled trials (Jadad score ≥ 3). A similar approach was adopted in another review, which has been submitted for publication (Hempenstall *et al.*, submitted). We also briefly comment on some open-label studies and suggest a treatment algorithm for PHN (Table 1).

In most clinical trials on PHN, the primary outcome measure is that of total pain. Few studies attempt to analyze the efficacy of the treatment on allodynia and itch, which are common features of PHN. We are not aware of published reports in which an attempt has been made to systematically measure evoked pain, or a study in which patients were enrolled on the basis of the presumed pathophysiology of their PHN, to match the pharmacologic mechanism of action of the drug. Petersen *et al.* [24•] have suggested that a topical capsaicin challenge test could be used to identify PHN patients in whom the mechanism of pain involves sensitization of peripheral afferents. Even good-quality studies on the treatment of PHN cannot avoid the common shortcomings of clinical trials, which are short follow-up, stringent inclusion criteria, and superficial assessment of effect on sleep, mood, and quality of life. In the case of PHN, there also are very few comparative trials and no trials in which the design is aimed at maximal efficacy from combination therapy.

Antidepressants

Several randomized, controlled trials have uniformly concluded that the tricyclic antidepressants (TCAs) amitriptyline [25–29], nortriptyline [29,30••], and desipramine [30••,31] and the second-generation antidepressant maprotiline [27] are effective in PHN with a groupwise number needed to treat (NNT) of 2.64 (95% CI, 2.1–3.5; Hempenstall *et al.*, submitted). They appear to relieve different types of pain (*ie,* spontaneous [constant, lancinating] and evoked pain), although few studies have attempted to measure this systematically [27,28]. It generally is accepted that the mechanisms of action of TCAs on pain are multiple and include inhibition of the reuptake of norepinephrine and serotonin in the central nervous system and blockade of sodium channels, *N*-methyl-D-aspartate (NMDA) receptors, and adrenergic receptors on the primary afferent [23]. Because nortriptyline is as effective as amitriptyline but better tolerated [28], it should be considered the preferred TCA for PHN, with desipramine remaining an alternative for those who experience excessive sedation with nortriptyline. The dose of TCAs in various clinical trials has varied between 10 and 250 mg. The median dose of nortriptyline was 75 mg [26] or 100 mg in [27] two substantive studies. In practice, individual tolerability is quite variable and dictates what dose is prescribed; long-term TCAs should be initiated at low doses (10–25

mg in a single dose taken at bedtime) and then slowly uptitrated, as tolerated. The most common side effects are dry mouth, constipation, sweating, dizziness, disturbed vision, drowsiness, and urinary retention. The well-known cardiac toxicity of TCAs should be kept in mind when treating older patients. Some authors recommend a screening electrocardiogram as a precaution to check for cardiac conduction abnormalities before commencement of TCA treatment. Despite these caveats, the TCAs remain an attractive treatment option for PHN because of their indisputable efficacy and low price.

Gabapentinoids

Gabapentin [32,33] and pregabalin [34•,35], which act by binding to the $a_2\delta$ subunit of voltage-dependent Ca^{2+} channels, have consistently shown efficacy in PHN, with an NNT of 4.4 and a 95% CI of 3.3 to 6.1 for gabapentin and 4.9 and 3.7 to 7.6, respectively, for pregabalin (Hempenstall *et al.*, submitted). In these trials, the dose of gabapentin varied between 1800 and 3600 mg and that of pregabalin between 150 and 600 mg [32,33,34•,35]. Both drugs also showed a favorable effect on sleep, mood, and quality of life, but their effect on different types of pain in PHN was not assessed. Gabapentin requires three doses daily. Similar to TCAs, the initial dose should be low (300 mg/d) with daily increments of 100 to 300 mg daily until a chosen target dose of 900 to 1800 mg daily has been achieved. Higher doses up to 3600 mg daily can be considered depending on tolerability. Pregabalin is administered twice daily, starting from 75 to 150 mg daily and increasing to a maximum of 600 mg daily. In the trials mentioned previously, approximately one third of patients taking pregabalin 600 mg daily [34•], one fifth taking pregabalin 300 mg daily, and one tenth taking pregabalin 150 mg daily withdrew [35]. In the former study, a significantly greater pain relief with pregabalin compared with placebo was found on the second day of the trial [34•]. Both drugs have a similar side-effect profile, with dose-dependent central nervous system effects (*ie*, dizziness, somnolence, and problems with cognitive function) predominating. Other common side effects include weight gain, peripheral edema, and dry mouth. Gabapentinoids are not protein-bound and are eliminated by renal excretion and have minimal interaction with other drugs. The dose must be adjusted in patients with renal insufficiency. The rapid commencement of effect and more dose-proportional pharmacokinetics are considered an advantage of pregabalin over gabapentin, but there is no evidence to date that the former has better overall efficacy or that there would be any benefit from switching patients on existing gabapentin to pregabalin.

Topical treatments

Following evidence from a small trial that topical lidocaine, when used as a 5% gel under occlusive dressing, reduces pain and allodynia in PHN [36], a more convenient method for applying lidocaine was developed in the form of a patch. This comprises a skin-friendly, self-adhesive surface, impregnanted with 5% lidocaine, which is placed on the painful area. Two early controlled trials, one employing an enriched enrolment method, demonstrated its efficacy over placebo [37,38]. Only patients with allodynia were included in these studies. A larger European trial that included patients with neuropathic pain, including 22 analyzable patients with PHN, later showed similar results [39]. Topical lidocaine is well tolerated; the only reported side effects are topical irritation and discomfort during patch application and removal. Because it produces clinically insignificant serum levels, it is thought to relieve pain by reducing ectopic discharges in the affected peripheral afferent fibers by blocking upregulated Na^+ channels. Depending on the size of the painful area, one to three patches are attached on the painful area for 12 hours each day. In a large, open-label study, the effectiveness of lidocaine patch was maintained for 28 days [40], but more long-term results have not been reported. The role of the patch on the therapeutic scene has not been established, but its peripheral mode of action offers an obvious opportunity for combined treatment with an oral preparation. Due to its safety and tolerability, the lidocaine patch was recommended as a first-line agent for PHN [23,40]. However, it is not available in most European countries.

Topical capsaicin has been studied in two good-quality randomized, controlled trials [41,42] in which concentrations of 0.025% and 0.075%, respectively, were compared with placebo. The intense burning sensation caused by capsaicin is likely to have compromised blinding in these trials. Burning pain on application, sensitization to heat, and irritation of the affected skin are typical side effects and a common cause for poor compliance. Increased pain is caused by capsaicin-induced stimulation of TRPV1 receptors on primary afferent endings, whereas the long-term effects likely are due more to the neurotoxic effects of the agent [43]. The efficacy of topical capsaicin from the two studies appears limited; the decrease of pain intensity was a maximum of 23% in one trial [42] and 30% in another [41]. Nevertheless, the estimated NNT is 3.3 (95% CI, 2.3–3.9; Hempenstall *et al.*, submitted). A trial was conducted recently (published in abstract form only) regarding 38 patients with PHN using 8% topical capsaicin in conjunction with local anesthetic. One single treatment led to a pain relief of 33% compared with placebo and this effect lasted for a follow-up period of 4 weeks. In a small, open-label extension study, this degree of pain relief was maintained by up to four top-up treatments [44]. The results of the latter study suggest that the true potential of capsaicin in PHN may not have been realized and larger similar controlled studies are warranted.

In a placebo-controlled, randomized, single-session trial, aspirin/diethyl ether cream was found to be superior to topical indometacin/diethyl ether and diclofenac/diethyl ether [45]. The proposed mechanism of action for this treatment is uncertain. There are no long-term results published. Compared with more user-friendly topical

treatments, notably the lidocaine patch, these preparations are difficult for the patients to use and the added ether in the mixture is a further concern for the prescriber and pharmacy.

Opioids

Previous controversy over the efficacy of opioids in neuropathic pain has been settled following compelling evidence from randomized, controlled trials in a number of conditions, including PHN. Tramadol, a centrally acting μ opioid agonist and a reuptake blocker of serotonin and noradrenalin, was shown to be effective in a placebo-controlled trial of 127 patients with PHN, with the reported NNT of 4.8 (95% CI, 3.5–6.0) [46]. The puzzling feature of this study was the dramatic improvement of pain in both groups (the mean pain level more than halved in the placebo group). Because of this, there was no change in the quality-of-life scores between the groups. However, there was a significant difference in the primary outcome measure, the global pain visual analog score, in favor of tramadol in per-protocol and intent-to-treat analyses at 6 weeks. The mean dose (SD) of tramadol was 275 mg daily. In general, tolerability was good and only nausea and constipation were more common in the tramadol group.

Oxycodone, morphine, and methadone have shown efficacy on PHN in two randomized, controlled trials [30••,47]. In a report on 38 patients with PHN, controlled-release oxycodone with a mean dose of 45 mg (SD, 17mg) daily reduced steady pain, paroxysmal pain, and allodynia significantly more than placebo, with 58% of the patients on oxycodone claiming at least moderate pain relief [47]. Disability scores were improved, without concomitant change in mood. Approximately one third of patients enrolled were already on TCAs and the analysis was per-protocol rather than intent-to-treat, leaving some uncertainty regarding the real effect. A very ambitious study design involving a randomized, two-stage crossover among an opioid, TCA, and placebo with a back-up alternative from each category enabled a rare head-to-head comparison between two active drugs [30••]. Patients were commenced on slow-release morphine, nortriptyline, or placebo. In the case of poor tolerability, morphine could be switched to methadone and nortriptyline to desipramine. Dose titration was individualized. The mean dose for morphine was 91 mg daily (range, 15–225 mg/d), for methadone, 15 mg daily, for nortriptyline, 89 mg daily, and for desipramine, 63 mg daily. A trend was shown toward greater reduction of pain with opioids compared with TCAs, but this may not be clinically significant. There was no correlation between opioid and TCA effect, suggesting that they control pain by unique rather than shared mechanisms. There were significantly more withdrawals during the opioid arm compared with the TCA arm. However, cognitive deterioration was found with TCA only. Of those patients who did not withdraw in any phase of the study, more subjects preferred opioids to TCA.

The combined NNT for strong opioids in PHN is estimated at 2.7 (95% CI, 2.1–3.8; Hempenstall *et al.*, submitted). The most common side effects of opioids are constipation, sedation, and nausea. The criteria for the use of strong opioids in chronic nonmalignant pain have been published [48]. Differently from TCAs, there is a dearth of long-term follow-up studies [30••]. Patients with PHN are, on average, elderly and polypharmacy is common, which makes long-term treatment particularly demanding. One of the more substantive follow-up series comes from Toronto where Watson *et al.* [49•] reviewed the outcome of 102 patients with nonmalignant chronic pain, mostly neuropathic, after a median of 8 years. The combined NNT for strong opioids in PHN is estimated to be 2.7 (95% CI, 2.1–3.8) [49•]. In this cohort, there were 15 patients with PHN. Although they were not reported separately, the overall results were impressive, with the effect maintained at a stable dosage level for a median of 3 years, tolerable side effects, and decreased disability. Of the total patient population, 11% showed drug-seeking behavior, all of whom had a history of chemical dependency.

Other treatments

Intrathecal methylprednisolone has been studied in two randomized trials. The first compared intrathecal and epidural administration of methylprednisolone with four weekly doses of 60 mg. The intrathecal route proved effective at 1 and 24 weeks [50]. In the latter larger study, which included 277 patients with established PHN for more than 1 year, patients were randomized to receive 3% lidocaine (3 mL) and methylprednisolone (60 mg) intrathecal, only 3% lidocaine (3 mL) intrathecal alone, or neither (but nevertheless underwent lumbar puncture) in four weekly sessions [51•]. Ninety percent of the methylprednisolone group had good to excellent pain relief, which continued through the 2-year follow-up as opposed to 7% in the lidocaine-only group, yielding an NNT of 1.13 (1.05–1.22; Hempenstall *et al.*, submitted). There also was a dramatic effect on mechanical allodynia. No neurotoxic effects were observed clinically or shown on magnetic resonance imaging. There are no published corroborative data and this poses a clinical dilemma to practitioners who are aware of the potential risks of intrathecal administration of methylprednisolone, compounded by warnings from the manufacturer.

Oral acyclovir, NMDA antagonists dextromethorphan and memantine, lorazepam, fluphenazine, benzydamine cream, and iontophoresis of vincristine are ineffective in PHN (Hempenstall *et al.*, submitted) [22].

Sympathetic and somatic nerve blocks have little value in fully established PHN and evidence for their use is conspicuously lacking [15,17]. The same is true of transcutaneous electric nerve stimulation (TENS). Although commonly used as an adjunct therapy, there are insufficient data to determine whether TENS is beneficial in chronic pain.

Spinal cord stimulation was suggested as a valid treatment choice for medically intractable PHN [52]. A subsequent case series of 28 patients reported good results of spinal cord stimulation in patients with PHN; long-term pain relief was achieved in 82% [53]. However, all of the patients belonged to the "irritable nociceptor" category [11••] with well-preserved sensory function in the affected area. Exclusion of patients with a deafferentation type of PHN may have contributed to these results. Thirty percent of the patients spontaneously improved during a median follow-up of 29 months. Kumar *et al.* [54] reported a failure in six of eight patients over a follow-up of 87 months and all of these patients were elderly. Two of four patients failed within 2 years in another series [55]. Holsheimer [56] reported on poor results following ganglion Gasseri stimulation in trigeminal PHN and concluded that the relief obtained from this form of stimulation is inversely correlated with the degree of sensory loss.

For intractable deafferentation-type cases of PHN, various neuroablative approaches have been used, including dorsal root entry zone, spinal trigeminal nucleotractotomy, and stereotactic radiosurgery of the trigeminal root. Although the series are small, the crude outcome appears to be that one third to 50% patients may experience satisfactory pain relief for 2 or 3 years postoperatively. Although the results are far from optimal, these procedures may be contemplated in centers with experience in stereotactic surgery and assessment of patients with chronic pain.

Conclusions

Pharmacotherapy remains the mainstay of treatment in PHN, with gabapentin, pregabalin, TCAs, opioids, and topical lidocaine or capsaicin showing efficacy in controlled trials. Intrathecal methylprednisolone/lidocaine combination appears very effective, but the published results await corroboration from other centers. No support can be provided for the use of sympathetic or spinal nerve blocks and the role of neurosurgical treatment is not established. Prevention of chronic PHN has proved difficult, although antiviral medications undoubtedly have an impact.

The first prospective, controlled trial involving a drug combination was published after the completion of this article by Gilron *et al.* [57].

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