Efficacy and Safety of Neuromodulators in Inflammatory Arthritis: A Cochrane Systematic Review

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ABSTRACT. ***Objective.*** To determine the efficacy and safety of neuromodulators for pain management in patients with inflammatory arthritis.

Methods. A Cochrane systematic review was performed as part of the 3e Initiative on pain management in inflammatory arthritis. We searched Medline, Embase, and Cochrane Central for studies to November 2010, and American College of Rheumatology/European League Against Rheumatism meeting abstracts published in 2008–2009. Studies were included if they were randomized or quasirandomized controlled trials that compared any neuromodulator (excluding cannabis) to another therapy (active or placebo, including nonpharmacological therapies) for pain in patients with RA, psoriatic arthritis, ankylosing spondylitis, or spondyloarthritis. Primary outcomes of interest were patient-reported pain relief of 30% or greater and withdrawals due to adverse events. Two authors independently extracted data and assessed methodological quality. A risk of bias assessment was performed using the methods recommended by the Cochrane Collaboration.

Results. Three trials, all in RA and all at high risk of bias, were included in this review. Two placebo-controlled trials evaluated nefopam (52 participants) and one placebo-controlled trial evaluated topical capsaicin 0.025% (31 participants). Pooled analysis showed a significant reduction in pain levels favoring nefopam over placebo after 2 weeks [weighted mean difference –21.2, 95% CI –35.6 to –6.7; number needed to treat (NNT) 2, 95% CI 1.4 to 9.5]. However, nefopam was associated with significantly more adverse events (RR 4.1, 95% CI 1.6 to 10.7; number needed to harm 9, 95% CI 2 to 367), predominantly nausea and sweating. In one trial, capsaicin reduced pain more than placebo at 1 and 2 weeks (MD –23.8, 95% CI –44.8 to –2.8; NNT 3, 95% CI 2–47, and –34.4, 95% CI –54.7 to –14.14; NNT 2, 95% CI 1.4 to 6, respectively). Of those who received capsaicin, 44% developed burning at the site of application and 2% withdrew as a result.

Conclusion. Based on 3 small trials, which were all at high risk of bias, there is weak evidence that nefopam and capsaicin are superior to placebo in reducing pain in patients with RA, but both are associated with a significant side effect profile. There are no available data for other types of IA or for newer agents such as gabapentin or pregabalin. (J Rheumatol Suppl. 2012 Sept;90:28–33; doi:10.3899/jrheum.120339)

Key Indexing Terms:
RHEUMATOID ARTHRITIS SYSTEMATIC REVIEW NEFOPAM CAPSAICIN

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The management of pain remains an important, yet often suboptimal, aspect of care in patients with inflammatory arthritis (IA). With widespread repercussions that affect quality of life, even seemingly small changes in pain intensity may have a strong influence on the perceived health in these patients. In recent times there has been growing interest and substantial progress in our understanding of the underlying mechanisms of chronic pain. However, deciding on an optimal pain management strategy for an individual with IA is not easy, and when initial standard treatments for pain fail, physicians may consider a broader scope of pharmacologic agents. With the unravelling of the complex interplay between the neural and immune systems in the genesis of pain, neuromodulators have received increasing attention as analgesics. The evidence base for their use, however, is less clear.

Neuromodulators are broadly defined as substances that alter nerve impulse transmission. Commonly used neuromodulators in pain management include anticonvulsant agents, ketamine, nefopam, capsaicin, and cannabinoids. More

recently botulinum toxin has also been studied in trials on a variety of pain states[1,2].

Although anticonvulsant drugs have been used in pain management for over 50 years, their precise mechanisms of action remain unclear. With wide variation in chemical structure, mechanism of action, and therapeutic properties, they are known to depress abnormal neuronal discharges and raise the threshold for propagating neural impulses. In addition, they may also enhance gamma-aminobutyric acid inhibition, stabilize neuronal cell membranes, and activate N-methyl-D-aspartate (NMDA) receptor sites[3]. NMDA receptor activation is also thought to be necessary for central sensitization. Clinically available NMDA antagonists include dextromethorphan and ketamine, although they have a variety of neuropsychiatric side effects that limit their clinical usefulness[4]. Commonly used anticonvulsant agents include gabapentin, pregabalin, phenytoin, sodium valproate, lamotrigine, carbamazepine, levetiracetam, oxcarbazepine, tiagabine, and topiramate. However, their use is not without risk: serious adverse effects include a report of deaths from hematological reaction[5].

Another centrally acting agent, nefopam, is used, mainly in Europe and New Zealand, as a potent non-opioid analgesic to improve postoperative pain[6]. It has also been used in rheumatic disease and other musculoskeletal disorders in the UK. The exact mechanism of action of nefopam's analgesic properties remains unknown. It is a centrally acting antinociceptive compound with supraspinal and spinal sites of action[7] that does not bind to opiate receptors[8]. It inhibits the reuptake of monoamines[9], modulates descending serotoninergic pathways[10], and may also interact with the dopaminergic pathway[11]. Nefopam is generally considered to be safe and well tolerated, with reported adverse effects most commonly including drowsiness, nausea and vomiting, and sweating. Potentially more serious adverse effects can occur including confusion, anaphylaxis, and tachycardia[12].

Capsaicin is an ingredient in chilies that inhibits the neuropeptide pain mediator named substance P. Topical application has been shown in placebo-controlled studies to relieve joint pain and tenderness in patients with arthritis[13], as well as postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, and reflex sympathetic dystrophy[14,15]. Sprays containing capsaicin are also used as riot control and personal defence agents. Adverse events commonly include a minor cutaneous burning sensation at the site of local application that is usually well tolerated. Cough has also been reported in about 8% of patients using the stronger 0.075% cream. Eye exposure leads to intense tearing, pain, conjunctivitis, and blepharospasm. If it is ingested in large quantities it can cause nausea, vomiting, abdominal pain, and burning diarrhea.

Botulinum toxins (BT) are potent neurotoxins produced by *Clostridium botulinum* that can block acetylcholine release at the neuromuscular junction and interrupt neuromuscular transmission. It has been shown to have an analgesic effect in patients with focal peripheral neuropathic pain and allodynia[16] and in diabetic neuropathic pain[17]. BT is currently used for strabismus and blepharospasm, cervical dystonia, primary axillary hyperhidrosis, focal spasticity, for cosmetic reasons[18], and more recently in refractory joint pain[19]. In the systematic reviews of BT for cervical dystonia, adverse events that were significantly more frequent than placebo injection with BT included neck weakness, dysphagia, dry mouth, sore throat, and hoarseness[20,21].

Despite more frequent prescription, there is a paucity of information to guide physicians in the safe use of neuromodulators in patients with RA. This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Pain Management by Pharmacotherapy in Inflammatory Arthritis[22]. The objective of this report was to systematically review the available literature concerning 1 of 10 selected questions as an evidence base for generating the recommendations: "What is the effectiveness, safety and role of (antidepressants, muscle relaxants) and neuromodulators in inflammatory arthritis (IA), and how should they be administered (i.e., interval, safety, and route)?"

This article is a modified version of a Cochrane review that is specifically focused on rheumatoid arthritis (RA)[23].

METHODS

The systematic literature review was carried out in several steps in accordance with the methods recommended by the Cochrane Collaboration[24].

Rephrasing the research question. The clinical question posed by the expert clinicians was rephrased to enable epidemiological enquiry using the PICO (Patient, Intervention, Comparator, Outcome) method[25]. Patients were defined as adults with RA, psoriatic arthritis, ankylosing spondylitis (AS), or spondyloarthritis. The intervention was defined as treatment with any formulation or dose of a neuromodulator as either monotherapy or in combination. Cannabis was excluded from this review. Comparators included placebo or any other pharmacological [excluding disease-modifying antirheumatic drugs (DMARD)] or nonpharmacological analgesic modalities. The primary outcomes of interest were pain and withdrawals due to adverse events, including mortality. The literature search was limited to randomized controlled trials, including trials where treatment was allocated via a quasirandom method.

Systematic literature search. A literature search for articles published between 1950 and May 2010 was performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials. The search strategy was developed in collaboration with an experienced librarian; for details see the online Appendix available from www.3epain.com. In addition, a search was conducted of abstracts from the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) scientific meetings in 2008 and 2009. Review articles were also retrieved for identifying additional references via hand search.

Selection of articles. The titles and abstracts of all studies identified by the search strategy were screened, and all potentially eligible studies were reviewed in full text by 2 authors (BR and SW). Studies were excluded if they contained a mixed population where the data of those with IA could not be extracted separately, or if they were written in languages that could not be translated by one of the members of the 3e Initiative multinational panel. Drugs that had been withdrawn from the market due to safety concerns were excluded from the review. Any disagreement in study selection was resolved by consensus or by discussion with a third reviewer (RB).

Data extraction and quality appraisal. Raw data were extracted from the included studies by 2 authors (SW and BR), using predetermined forms.

Differences in data extraction were resolved by referring back to the original articles and establishing a consensus. A third reviewer (RB) was consulted to help resolve differences as necessary. Two authors (SW, BR) independently assessed risk of bias for all included studies for the following items: random sequence generation, allocation concealment, blinding of participants, care provider, outcome assessor for each outcome measure, incomplete outcome data, and other biases, according to the methods recommended by the Cochrane Collaboration[20]. To determine the risk of bias of a study, each criterion was rated as Yes (low risk of bias), No (high risk of bias), or Unclear (either lack of information or uncertainty over the potential for bias).

Data analysis. For continuous data, results were analyzed as mean differences between the intervention and comparator group (MD) with 95% confidence intervals (CI). When plausible, results from similar studies were pooled and reported as a weighted mean difference (WMD). However, when different scales were used to measure the same conceptual outcome (e.g., pain), standardized mean differences were calculated. For dichotomous data, a relative risk (RR) with corresponding 95% CI was calculated. In cases where individuals were missing from the reported results, we assumed the missing values to have a poor outcome. Prior to metaanalysis, we assessed studies for clinical homogeneity, and where studies were sufficiently homogeneous that it remained clinically meaningful for them to be pooled, a metaanalysis was performed using a random-effects model. Statistical heterogeneity was assessed using the I^2 statistic[26]. In addition to the absolute and relative magnitude of effect, for dichotomous outcomes, the number needed to treat (NNT) to benefit or the number needed to treat to harm (NNTH) were calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator (available from http://www.nntonline.net/visualrx/). Analysis was performed using Review Manager 5.

RESULTS

Study characteristics. A total of 1146 references were identified with the systematic search strategy. Removal of 139 duplicates left 923 abstracts for review. Of these, 41 studies were assessed for detailed review, of which 3 studies fulfilled our selection criteria (Figure 1, Table 1). A review of the last 2 years of ACR and EULAR abstracts and references did not find any further relevant studies.

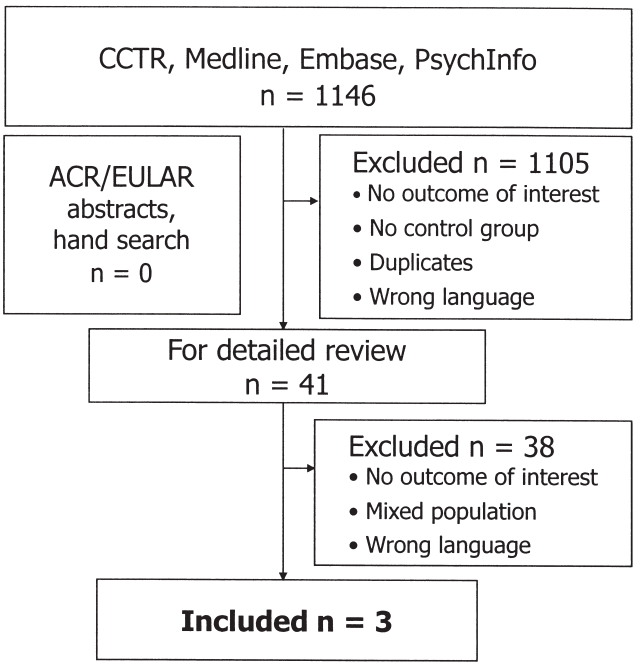

Figure 1. Literature search from which 41 articles were selected for detailed review. Three articles met the inclusion criteria.

Of the 3 studies deemed to meet inclusion criteria[27,28,29,30], 2 trials evaluated the centrally acting analgesic drug nefopam[27,30], and one assessed topical capsaicin[29]. All 3 trials had high risk of bias (Figure 2).

Two crossover trials (52 participants) evaluated nefopam in the same dose (60 mg, 3 times daily) against placebo over 2 weeks (n = 27)[30] and 4 weeks (n = 25)[27]. Only Emery and Gibson 1986[27] included a 1-week washout period before each active treatment phase. Both studies were performed in the UK and published in the late 1980s. Participants were outpatients who met the ACR criteria for RA and had persistent pain. Neither study reported any specific information about the type of pain participants were experiencing. The majority of patients were women (83%) and they were generally receiving maximal doses of nonsteroidal antiinflammatory drugs (NSAID), with 51% of the Emery and Gibson[27] study also taking a variety of DMARD (gold, penicillamine, chloroquine, or prednisone). Co-interventions were not reported in the Swinson, *et al* 1988 trial[30]. Pain was reported using a 100-mm visual analog scale (VAS) for both trials, with Swinson, *et al*[30] specifically measuring night pain, and Emery and Gibson measuring pain in general.

One trial evaluated 0.025% topical capsaicin (4 times daily) versus a placebo vehicle cream on knee pain[29]. This US study was conducted in patients with osteoarthritis (OA; 70 participants) and RA (31 participants), with the efficacy data presented separately. Participants were predominantly female (81%), mean age 54 years (range 20–79), with moderate to severe knee pain (mean VAS 56 mm). No patient had received intraarticular corticosteroid injection in the preceding 3 weeks, and 84% were taking NSAID, 32% corticosteroids, 13% gold, and 10% other immunosuppressive agents. The primary outcome measure was pain intensity on a 100-mm VAS. The study was hampered by the inherent difficulties of truly blinding patients receiving capsaicin who experience a characteristic local burning sensation.

The predominant methodological flaws of the included trials included failure to describe randomization, allocation concealment, compliance, and adequate blinding of study personnel and patients. There were also high dropout rates, and no study performed an intention-to-treat analysis. The included trials did not record the concomitant use of other analgesic agents, and did not describe how missing data were dealt with.

Primary outcomes. Nefopam versus placebo. Two studies with high risk of bias assessed pain outcomes in patients receiving oral nefopam 180 mg daily and reported conflicting outcomes[27,30]. Both studies used a crossover design; however, only Emery and Gibson[27] had a washout period before each active treatment was given. Neither study reported the primary outcome measure of patient reported pain relief of 30% or greater. Emery and Gibson reported a significant reduction in mean pain intensity (VAS 100 mm) compared to placebo

Table 1. Characteristics of included studies.

Study	Population	Intervention	Comparator(s)	Outcome(s)	Study Design
Emery 1986[27]	27 patients with RA, mean age 59 yrs, disease 4-30 yrs, 51% receiving gold, penicillamine, chloroquine, or prednisone Exclusion: not specified	Nefopam 60 mg tds	Placebo	Primary: 1. Pain (VAS 100 mm) 2. EMS (VAS 100 mm), 3. Joint tenderness, 4. Grip strength 5. PIP size	Crossover Trial, double blind, 4 weeks
Swinson 1988[30]	`25 patients with RA, mean age 58 yrs (35-71), mean duration RA12.6 years (2-30), most patients taking NSAID , Exclusion: information not specified	Nefopam 60 mg tds	Placebo	Primary: 1. Pain (VAS100 mm) 2. EMS (min), 3. Grip strength, 4. Ring size	Crossover trial, double blind, 2 wks
Deal 1991[29]	31 patients with RA, mean age 20-79, mean pain 55-57 (VAS 100 mm) 84% taking NSAID, 32% corticosteroids, 13% gold, 10% other immunosuppressive agent Exclusion: Intraarticular corticosteroid injection ≤3 wks, topical corticosteroids ≤ 7 days prior to study onset, skin disorder in affected knee	Topical 0.025% capsaicin	Placebo vehicle cream	Primary: 1. Pain intensity (VAS 100 mm), 2. Pain relief (VAS 100 mm), 3. Physician Global Response	RCT, double blind 6 wks

NSAID: nonsteroidal antirheumatic drugs, VAS: visual analog scale; EMS: early morning stiffness; PIP: proximal interphalangeal joint; RCT: randomized controlled trial.

	Deal 1991	Emery 1986	Swinson 1988
Adequate sequence generation?	?	?	?
Allocation concealment?	?	?	?
Blinding?	x	?	?
Incomplete outcome data addressed?	?	✓	✓
Free of selective reporting?	✓	✓	✓
Compliance?	✓	?	?
Cointerventions?	?	?	✓
Were baseline characteristics similar?	✓	✓	?
Was an intention to treat analysis performed?	x	x	x
Was there a high drop out rate?	✓	✓	x
Summary assessment of bias	x	x	x
x: high risk of bias, ✓:low risk of bias, ?: unclear risk of bias.			

Figure 2. Risk of bias summary: authors' judgments about each risk of bias item for each included study.

after 2 weeks (MD of –21.16, 95% CI –35.61 to –6.71) and 4 weeks (MD –25, 95% CI –42.22 to –7.78). In contrast, Swinson, *et al*[30] reported no significant difference after 2 weeks' treatment in night pain on a 100-mm VAS (MD –12.00, 95% CI –38.59 to 14.59). That study was biased by the high dropout rate, making meaningful interpretation difficult. When data were pooled using a random effects model, there was still a significant reduction in pain levels favoring nefopam (WMD –21.16, 95% CI –35.61 to –6.71) with statistical homogeneity ($I^2 = 0$, $p = 0.42$). Using the Emery and Gibson study for the baseline control group SD and a minimal clinically important difference (MCID) of 15 mm, the NNT was 2 (95% CI 1.4 to 9.5).

Only the Emery and Gibson study reported data withdrawals due to adverse events. Five patients in the nefopam group withdrew after developing nausea, with no withdrawals in the placebo group. This small trial showed a trend favoring placebo but did not reach statistical significance (RR 11.00, 95% CI 0.64 to 189.65). Swinson, *et al*[30] reported that 12 patients dropped out, but did not describe which treatment

they had received. Both trials reported adverse event data, with only Emery and Gibson showing a statistically significant increase in adverse events in the nefopam group (RR 4.11, 95% CI 1.58 to 10.69), yielding a NNTH of 9 (95% CI 2 to 367). These were predominantly nausea (56%), sweating (44%), insomnia (11%), pruritis (11%), and malaise (11%).

Topical capsaicin versus placebo. Deal, *et al*[29] used 2 separate measures to evaluate pain (percentage reduction of pain using a VAS 100 mm and categorical scale). Overall, both scales reported a statistically significant improvement in pain favoring topical use of 0.025% capsaicin at 2 weeks only. Using the VAS 100 mm, there was a significantly greater reduction in pain favoring capsaicin at 1 and 2 weeks (MD –23.80, 95% CI –44.81 to –2.79, and MD –34.40, 95% CI –54.66 to –14.14, respectively). This corresponded to a NNT 3 (95% CI 2 to 47) at 1 week and NNT 2 (95% CI 1.4 to 6) at 2 weeks. There was only a trend towards improvement at 4 weeks (MD –25.00, 95% CI –51.76 to 1.76). With the categorical scale there was only a statistically significant difference at 2 weeks (MD –0.60, 95% CI –0.99 to –0.21) with a trend towards improvement at 1 week (MD –0.37, 95% CI –0.77 to 0.03) and 4 weeks (MD –0.47, 95% CI –1.08 to 0.14). These discrepancies were likely related to Type II error.

No data regarding withdrawal due to adverse events could be extracted for the RA population. Two patients withdrew after 2 weeks of capsaicin treatment due to burning at the site of application, but it was unclear if these patients were from the RA or OA population. Similarly, no data were extracted regarding total adverse events. The only adverse reaction reported to be attributable to the intervention was the presence of burning at the site of application. This occurred in 44% of the trial patients receiving capsaicin (and 1 patient in the placebo group), but it was unclear what proportion of patients with RA were affected. There were no serious adverse events.

DISCUSSION

This is the first systematic review to assess the efficacy and safety of neuromodulators for treating pain in patients solely with IA. Our results review served as an evidence base for one of the 10 recommendations regarding pain management by pharmacotherapy generated by a multinational panel of rheumatologists as part of the 3e Initiative. A detailed description of all final recommendations can be found elsewhere[22].

We identified 3 randomized trials with high risk of bias evaluating the use of neuromodulators for pain management in patients with IA. Overall, limited data suggest that nefopam and topical capsaicin are superior to placebo in reducing pain in patients with RA. However, each agent is associated with a significant side effect profile that may offset the benefits.

There is weak evidence that nefopam has analgesic efficacy compared with placebo in patients with RA who are not taking other analgesic medications over 4 weeks. The magnitude of this benefit was on average 21.16 points on a 100-mm VAS scale. The NNT to achieve a positive result from these studies at 2 weeks was 2 (95% CI 1.4 to 9.5). Any benefit in pain levels may be limited by nefopam's side effect profile. Nausea is a well known side effect and was the predominant reason for withdrawal in the included studies, with around 1 in 5 patients ceasing the drug as a result. Given the small number of participants, withdrawals due to adverse events did not reach statistical significance; however, there was a strong trend towards increased risk with nefopam (RR 11.00, 95% CI 0.64 to 189.65). Total adverse events were significantly more common with nefopam and consisted of nausea, sweating, insomnia, pruritis, and malaise (NNTH 9, 95% CI 2 to 367). Although not seen in the included studies, potentially more serious adverse effects can occur, such as confusion and tachycardia.

The 2 nefopam trials were conducted in the 1980s in study populations that are not reflective of current patients with RA. In general, they had poorly controlled disease and were receiving only NSAID, with only occasional low-dose corticosteroid or DMARD. No patients were receiving biological therapy. Our safety results (NNTH = 9) are similar to those of a recent systematic review in postoperative patients that included 9 randomized trials (n = 847), which found there was some evidence that nefopam reduced postoperative pain scores (WMD –11.5 mm, 95% CI –15.1 to –7.85), but subjects had increased tachycardia (NNH 7) and sweating (NNH 13)[12]. With many other safer analgesics available on the market today, and no head-to-head trials suggesting superior efficacy, our review does not support the routine use of nefopam in patients with RA.

Topical capsaicin may provide some relief in patients with RA with persistent knee pain, but at the expense of local skin irritation with associated burning and stinging. The confidence in our estimates is not strong, given difficulties with blinding, small numbers of participants evaluated, and a lack of adverse event data. Capsaicin was tested in 1 small trial in the lower (0.025%) of the 2 strengths (0.075%) currently available. After 2 weeks of treatment patients receiving capsaicin had less pain than those in the placebo group, with a mean improvement of 23.80 on a 100-mm VAS. The NNT to achieve this benefit was 2 (95% CI 1.4 to 6). Safety data regarding the RA population were not reported separately, so this review is unable to assess the safety of this medication in patients with RA. Overall, 44% of patients (with RA and OA) were reported to suffer mild or moderate local burning at the site of application, which is consistent with rates reported in other trials. A Cochrane Review recently assessed herbal therapy for treating RA[31] and 2 trials in their analysis[29,32]. We excluded the McCarthy, *et al*[32] trial as it contained a mixed population (OA and RA), and data were not able to be separately extracted for the RA group. Despite this, our results are similar to the observations made in that review in regard to both efficacy and relative safety.

There are several further limitations in the interpretation of the results of our review. Overall, the trials were small, of

short duration, and lacking in safety data. All the included studies had a high risk of bias and limited data, so no robust conclusions can be drawn from this review. A single new large study assessing any of the included drugs could significantly alter the efficacy estimates. The character of the pain was not described in any of the included studies, making it difficult to assess in which patients the data may be applicable. No study provided adequate data to address the primary efficacy outcome variable (> 30% improvement in pain) and none of the commonly used anticonvulsants (e.g., gabapentin or pregabalin) was evaluated.

In some patients, even a small degree of pain relief may be considered worthwhile. Overall, given the relatively mild nature of adverse events, capsaicin could be considered as an add-on therapy for patients with persistent local pain and inadequate response/intolerance to other treatments, who are able to tolerate the side effects. Oral nefopam, however, has a more significant side effect profile and the potential harms seem to outweigh any modest benefit achieved.

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