Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com

Movement disorders

Essential tremor: Update of therapeutic strategies (medical treatment and gamma knife thalamotomy)

T. Witjas [a,b,*], R. Carron [c,d], E. Boutin [a], A. Eusebio [a,b], J.P. Azulay [a,b], J. Régis [c,d]

[a] Neurology department, Timone university hospital, Aix-Marseille university, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France
[b] Institut de neurosciences de la Timone, UMR 7289, CNRS Aix-Marseille université, boulevard Jean-Moulin, 13005 Marseille, France
[c] Department of functional and stereotactic neurosurgery and radiosurgery, Timone university hospital, Aix-Marseille university, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France
[d] Inserm, UMR 1106, Aix-Marseille university, boulevard Jean-Moulin, 13005 Marseille, France

INFO ARTICLE

Article history:
Received 9 March 2016
Received in revised form
6 July 2016
Accepted 25 July 2016
Available online xxx

Keywords:
Tremor
Treatment
Surgery
Thalamotomy
Gamma knife radiosurgery

ABSTRACT

Tremor is a highly prevalent movement disorder that markedly reduces quality of life. The management of severe tremor is particularly challenging. Pharmacological treatment is available, but no real breakthrough has emerged recently. Propranolol and primidone are still the two most recommended agents, followed by topiramate. However, surgical treatments for medically refractory tremors are expanding. Gamma knife (GK) thalamotomy is an option particularly suitable for patients who are not candidates for deep brain stimulation. Owing to the fact that it is a non-invasive procedure without craniotomy, GK radiosurgery has almost no contraindications. Since the late 1990s, more than 250 case reports and patient series have been published. Most of these studies show that unilateral GK thalamotomy is well tolerated and reduces tremor disability. A recent study with prospective blinded assessment has confirmed its safety, together with significant improvements in tremor scores and activities of daily living.

1. Introduction

Tremor is a hyperkinetic movement disorder characterized by rhythmic oscillations of one or more body parts. It may be disabling and significantly impair quality of life. Yet, it is sometimes challenging to find the appropriate treatment to reduce disability [1]. In 2011, an expert committee of the American Academy of Neurology published an update of the 2005 evidence-based guidelines for the treatment of essential

* *Corresponding author*. Service de neurologie et pathologie du mouvement, CHU Timone, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France.
E-mail address: tatiana.witjas@ap-hm.fr (T. Witjas).
http://dx.doi.org/10.1016/j.neurol.2016.07.014

Table 1 – Pharmacological recommendations for essential tremor [2,16].

Level of evidence	Drug	Dosage (mg/day)	Efficacy (%)	Adverse events
A	Propanolol	40–320	50–60	Reduced arterial pressure, reduced pulse rate, tachycardia, bradycardia, impotence, drowsiness, exertional dyspnea, confusion, headache, dizziness
	Primidone	50–1000	50	Sedation, drowsiness, fatigue, nausea, giddiness, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, acute toxic reaction
B	Topiramate	50–400	22–37	Appetite suppression, weight loss, paresthesias, anorexia, concentration difficulties
	Atenolol	50–100	25–37	Lightheadedness, nausea, cough, dry mouth, sleepiness
	Sotalol	80–240		Decreased alertness
	Alprazolam	0.125–3	25–35	Fatigue, sedation, potential for abuse
	Gabapentin	1200–1800	33–77	Lethargy, fatigue, decreased libido, dizziness, nervousness, shortness of breath
C	Clonazepam	0.5–6		Drowsiness
	Clozapine	6.25–75		Agranulocytosis, drowsiness, sedation
	Botulinum toxin (cervical muscles)	NA		Neck weakness, postinjection pain
Recommendations against use	3,4-DAP, amantadine, acetazolamide, mirtazapine, levetiracetam, isoniazid			

NA: not available; DAP: diaminopyridine.

tremor (ET) [2]. Since 2011, however, few advances have been made in oral treatments of ET, and no new medication has reached level A recommendation.

2. Pharmacological treatments

Propranolol and primidone are still the most frequently used medications to treat ET and represent the most successful drugs for the condition. Propranolol is the only medication approved by the US Food and Drug Administration (FDA), whereas both drugs have applied for marketing authorization for ET to the European Medicines Agency (EMA). Efficacy and tolerability have been demonstrated by randomized double-blind studies for both medications (doses and side-effects are presented in Table 1), and they are effective in 50–70% of patients [3].

Of the other medications that can be used as second-line options, benzodiazepines and anticonvulsants are the most efficacious (Table 1).

Three randomized controlled trials, with a total of 294 participants, reported significantly better results with topiramate compared with placebo in reducing Fahn–Tolosa–Marin Tremor Rating Scale (TRS) scores, although a significant number of patients withdrew due to adverse effects (paresthesia, taste perversion, attention difficulties and memory complaints) [4–6].

The effect of zonisamide in ET has been investigated in two studies. One double-blind, placebo-controlled, parallel-design study using a mean dose 160 mg/day of zonisamide in 20 patients with ET showed no significant improvements in TRS scores, but there was a statistically significant 40% improvement in accelerometry [7]. The other one, an open-label study of 25 patients (mean dose: 252 mg/day) using blinded video assessment, showed an estimated percentage reduction of 41% for postural tremor and 46% for kinetic tremor [8]. Zonisamide therefore received a level U recommendation, as the results were inconclusive [2].

While pregabalin titrated to a maximum dose of 450 mg failed to significantly improve ET patients [9], ethanol has been reported to reduce tremor intensity in such patients. Octanoic acid is the active metabolite of long-chain alcohols. However, a phase-I/II study of 18 patients showed no efficacy in reducing tremor [10].

3. Local treatments

The efficacy of botulinum toxin type A (BTXA) has been examined in nine studies. Two reported mild improvement of postural tremor compared with a placebo, and a small improvement of kinetic tremor [11,12]. Given its local administration, BTXA is better indicated for head and voice tremors. One crossover study and one open-label study documented mild-to-moderate improvements in head tremor with BTXA; Pahwa and co-workers [13] noted moderate-to-marked improvements in five of 10 patients treated with BTXA compared with one of 10 patients treated with a placebo, although accelerometry did not change significantly. Two open-label studies of voice ET indicated beneficial effects in 67% of patients with bilateral BTXA injections into the vocalis muscle [14,15]. Weak voice, coughing, choking and dysphagia are common side-effects of laryngeal botulinum injections. As larger studies are needed, BTXA received a level C recommendation.

4. Surgical treatments

As pharmacological treatment of severe tremor is often disappointing—medications are not always well tolerated

Please cite this article in press as: Witjas T, et al. Essential tremor: Update of therapeutic strategies (medical treatment and gamma knife thalamotomy). Revue neurologique (2016), http://dx.doi.org/10.1016/j.neurol.2016.07.014