Mirtazapine in the treatment of essential tremor: an open-label, observer-blind study

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Introduction: Essential tremor (ET) is the most common movement disorder in the adult population. At present ET treatment shows limited efficacy, particularly in patients with severe and disabling symptoms. This study evaluates the clinical efficacy of mirtazapine in an untreated ET patient population.

Materials and methods: 30 ET patients (female/male = 19/11; average age = 71.4 ± 8.3 years) were examined by clinical criteria, electromyographic (EMG), and apomorphine tests to study the cortical silent period. The patients were all treated with mirtazapine 30 mg daily.

Results: Mirtazapine proved to be a good control agent for tremor symptomatology in 23/27 patients (85%) who completed 1 month of treatment, with a marked reduction of tremor; the benefit was maintained during the 12-month follow-up. No significant variation in EMG parameters was observed aside from two prevalent and distinct frequencies of tremors (5–6 Hz and 7–8 Hz) and a group of selected patients whose cortical silent period (SP) was markedly reduced. There were no clinical differences between the two subgroups. All apomorphine-tested patients showed an SP with no significant modifications.

Conclusions: Mirtazapine proved to be an efficacious drug treatment for tremor symptoms in patients suffering from ET. It had limited side effects and excellent overall tolerability, could be used as daily monotherapy, and did not interfere with any of the many other medications being taken simultaneously by the patients.

Keywords: essential tremor, postural tremor, action tremor, mirtazapine, treatment, transcranial magnetic stimulation

Introduction

Essential tremor (ET), along with Parkinson's disease, is a diagnosed extrapyramidal disorder resulting in the most common movement disorders in aging adults (Brin and Koller 1998). When it is the only neurological disorder in different members of the same family, generally with autosomal dominant transmission, it is defined as familiar or hereditary tremor. When diagnosed in old age it is also classified as senile tremor. ET is characterized by a monosymptomatic postural and/or kinetic tremor (4–8 Hz frequency) mainly related to the upper limbs symmetrically (in 10% of cases it can appear in the dominant hand); less frequently it can also occur in other parts of the body such as the head or it can affect the voice. The tremor is made worse by emotions, physical exercise, and tiredness. Both males and females are equally involved. The disease can occur even prior to the second decade of age but generally incidence and prevalence grow with age, mainly after the age of 40 (0.4%–6.7% prevalence in general population) reaching a specific age prevalence peak after the age of 60 (12% of population).

Traditionally, ET has also been called "benign" while actually showing a high degree of variability in development, ranging from the least symptomatic and

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evolutionary forms to the gradually progressive ones having a stronger postural and mostly kinetic component which seriously interferes with routine activities (about 10% of cases).

Due to its relatively high frequency and appearance in mature age, patients often reach the neurological center believing the tremor to be an early symptom of Parkinson's disease. A correct diagnosis can therefore reassure most patients on the nature and likely progression of the "tremor" symptom.

At present ET treatment is scarcely effective, especially for patients whose symptoms are seriously disabling. Only two drugs have been proven equally effective in ET therapy: propranolol (80–320 mg daily) and primidone (50–500 mg daily) (Wasielewski et al 1998; Louis 2001). However, only 50% of treated patients report a lasting benefit, and both drugs equally produce numerous side effects which, especially for primidone, entails low initial dosages that slowly and progressively increase to reach the optimal efficacious amount to be prescribed.

A second line of therapeutic approaches has been proposed which involves the use of clonazepam (Thompson et al 1984), alprazolam (Huber and Paulson 1988), gabapentin (Ondo et al 2000), methazolamide (Muenter et al 1991), clozapine (McCarthy 1994), nimodipine (Biary 1995), and theophylline (Mally and Stone 1991). Their effectiveness is, however, clinically insignificant and most of all transient.

Botulinum toxin type A, which produces sustained neuromuscular block (Jankovic et al 1996), proved temporarily useful in reducing tremor of the hands but such a result depends on exact choice of dosage, and number and point of injections, so as to reduce the risk of excessive focal muscular hyposthenia to a minimum. Finally, it should be kept in mind that even alcohol (Koller et Biary 1984) reduces ET. Alcohol would be difficult to propose and manage, for it might lead to addiction or abuse, although no increase in the rate of alcoholism has been shown in patients suffering from ET (Koller 1983).

A number of significant clinical cases initially reported (Pact and Giduz 1999; Gordon et al 2002) and some personal clinical experience suggested the potential efficacy of mirtazapine, an antidepressant that is the first in a line of specific noradrenergic and serotoninergic antidepressants (NaSSAs) in reducing tremor of patients suffering from extrapyramidal diseases. Mirtazapine acts as a central antagonist of noradrenaline $\alpha 2$ presynaptic receptors and increases noradrenergic and serotoninergic transmission while blocking the 5-HT2 and 5-HT3 receptors. A long plasma half-life (20–40 hours), rapid achievement of steady-state, and a high degree of tolerability, mainly for its negligible effects on the cardiovascular system, make the drug extremely manageable and suitable even for older patients.

Our study aimed at evaluating the clinical efficacy of mirtazapine in a population of patients affected by ET presenting for the first time for observation without other treatments for tremor.

Subjects and methods

A group of 30 patients (19 females, 11 males), aged 48–89 years (mean 71.4 ± 8.3 years) and whose clinical diagnosis of ET was in accordance with ET principal criteria, was included in the study. Their duration of illness was 1–40 years (mean 7.3 ± 9.4 years), and 12/30 (40%) showed a positive family association with ET. All patients were registered at the Neurological Operating Unit of the Busto Arsizio District Hospital near Varese (Unità Operativa di Neurologia dell'Ospedale di Circolo di Busto Arsizio, Varese, Italy).

Clinical evaluation consisted of anamnestic and neurological examination especially by observing extrapyramidal symptoms other than tremor as well as symptoms or signs of other "tremorgenic" neurological or internal pathologies.

Table 1 Primary, secondary, and key criteria in ET differential diagnosis

Primary criteria
– Bilateral action tremor of the hands and forearms (but no tremor while at rest)
– Lack of other neurological signs, except the "gear-wheel" phenomenon
– Isolated head tremor could be present, with no anomalous postures or dystonies
Secondary criteria
– Long period of time (> 3 years)
– Family history
– Reduction with intake of alcoholic beverages
"To be differentiated"
– Unilateral tremor, focal tremor, tremor of the legs, walking disorder, stiffness, bradykinesia, tremor at rest
– Sudden or rapid appearance
– Simultaneous therapy with tremor causing or tremor increasing drugs
– Isolated head tremor with anomalous postures (bending or rotation)

Adapted from: Elble (2000).

Table 2 Tremor rating scale

	0	1	2	3	4
A – Resting tremor	absent	slight, intermittent, small amplitude, hardly disturbing, controlled by will	moderate, constant, amplitude is variable but less than 50 mm, disturbing to the subject, can be controlled by will	serious, constant, amplitude ranging from 50 to 100 mm, very disturbing for the subject, only temporarily suppressed by will	very serious, constant, over 100 mm amplitude, disabling, hardly controlled by will
B – Postural tremor (Rated with glass full to the brim)	absent	slight, intermittent, small amplitude, hardly disturbing, no spilling from glass	moderate, constant, variable amplitude but still slight, not very disturbing for the subject, intermittent and slight dripping from glass	serious, constant, average amplitude interferes with many activities, constant dripping from glass	very serious, constant, considerable amplitude, hindering activities, marked dripping from glass
C – Action tremor **C1: in alternating flexion/extension arm movements** **C2: in reaching a target (index-nose test)**	absent	slight, intermittent, small amplitude, hardly disturbing, controlled by will	moderate, constant, amplitude is variable but less than 50 mm, disturbing to the subject	serious, constant, amplitude ranging from 50 to 100 mm, interferes with many activities	very serious, constant, over 100 mm amplitude, hindering activities
D – Orthostatic tremor	absent	slight, intermittent, small amplitude	slight, constant, with variable oscillations	moderate, constant, average amplitude, can interfere with balance	serious, constant, with broad oscillations, can be disabling
E – Tremor of the head	absent	slight and intermittent	slight but constant, not disturbing	moderate, constant, interferes with some activities	serious, constant, interferes with most activities
F – Speech	normal	slight tremor of the voice, not steady, no difficulty in making oneself understood	slight tremor of the voice, constant, occasional difficulties in making oneself understood (rarely needs to repeat sentences)	moderate tremor of the voice, pronouncing words distinctly now and then, constant, a few incomprehensible sentences need to be repeated	serious tremor of the voice, articulating words and not very understandable
G – Writing	normal	slightly impaired, but legible	moderately impaired, but every word is legible	seriously impaired, a few words illegible	illegible
H – Overall subjective disability	absent	slight, variable	slight, constant	moderate	serious

Adapted from Deuschl (1987).

The ET diagnosis formulated was in accordance with the guidelines established by the Tremor Investigation Group and by the Consensus Statement of the Movement Disorder Society (Deuschl et al 1998; Elble 2000) which point out "primary" essential criteria and "secondary" supporting criteria (Table 1)

All patients also underwent a biohumoral screening that included thyroid functioning as well as tremor "grading" carried out according to a 5-point rating scale (0–4) (Table 2). All evaluations were carried out by an examiner who was "blind" to the pharmacological treatment received by the patients. The scale used enabled study of the frequency, as well as the amplitude and the interference with activities, of the different kinds of tremor being examined. Resting tremor was rated as the patient sat comfortably on a chair with relaxed limbs. Postural tremor was rated with

stretched arms. Action tremor was studied while the patient performed an alternating flexion–extension movement of the arm and hand (simple action tremor) and differentiating it from tremor that might occur during the "index-nose" test performance (specific action tremor). Lastly, the patient was asked to evaluate subjectively the overall tremor-caused disability on the quality of his/her own life.

On completing the clinical study the patients were morphologically examined (computerized tomography or magnetic resonance) in order to exclude any significant alteration of the brain, and they also underwent electromyographic (EMG) tremor evaluation with surface electrodes of antagonist muscles (finger common flexor and finger common extensor, short abducent of the thumb and first dorsal interosseous) while at rest and when maintaining posture.

When examining patients whose sole extrapyramidal disorder is tremor, many studies have demonstrated that modifications occur both in the characteristics of the evoked potential motion (EPM) of the cortex and in the inhibiting phenomenon defined as the cortical silent period (SP) typical of the most important extrapyramidal syndromes. Such stimulating and inhibiting phenomena were thus evaluated and compared with the standard data we had acquired. The patients were therefore studied for their EPM and SP as well as the EMG tremor plot throughout the test, including evaluation of SP modification by the apomorphine test.

To carry out the EMG test a MAGSTIM model 200 magnetic stimulator (Magstim Company Ltd, Whitland, Wales, UK) was employed which had a "high power" 14-mm diameter coil located on the vertex with a counter-clockwise flux current. EMG activity was recorded on the subject while comfortably sitting, hands supine, tracing via Ag–AgCL surface electrodes from the short adductor of the thumb (SAT) and first dorsal interosseous, or from two antagonist muscles of the forearm (finger common flexor and finger common extensor) by means of a NICOLET VIKING 2 testing unit (Nicolet Biomedical Inc, Madison, WI, USA), processing the signal through a band passing filter between 20 and 2 Hz.

For the EPM tests, the optimal position on the scalp for stimulation was found by establishing the EPM having the greatest amplitude and highest stimulus output (80%–100% 1.5 Tesla). Subsequently, the stimulus was reduced to detect the threshold of EPM (the minimum stimulus intensity able to elicit an EPM of around 50–100 μV in about 50% of 10 consecutive responses, as suggested by Cantello et al (1991). The optimal position was usually situated 10–20 mm in front of and 50–60 mm on the side of the vertex while the coil was kept tangential to the scalp with an angle about 45° from the median line.

The measurement of the length of central, post-EPM SP was obtained by averaging 4–6 stimulations during a continuous tonic contraction corresponding to about 50% of the maximum strength of the target muscle (usually SAT) with the super maximal stimulus intensity (80%–100 %). Each stimulation was repeated alternately on both sides of the scalp shunting from counterlateral target muscles.

Domperidone (a specific peripheral antagonist of dopaminergic receptors unable to cross the hemato-encephalic barrier) was given by mouth in a dose of 20 mg thrice daily 3 days before going through the test, to prevent any possible side effect (nausea and vomiting) induced by apomorphine. The patient's clinical examination was carried out before and about 15, 20, and 30 minutes after the subcutaneous injection of 2 mg of apomorphine chlorhydrate (10 mg/mL), immediately following the recording of the SP.

After completing the diagnostic examination procedure, all patients were treated with mirtazapine 30 mg daily once in the evening, and they went through clinical re-examination and EMG check-ups 30 days after initiating the treatment. Those patients who responded to the treatment were re-examined again clinically 3 months later, and subsequently on a 3-monthly basis.

Statistical analysis of the non-parametric variables was performed by means of Wilcoxon's rank test. Parametric variables were compared by ANOVA. Statistical significance level was set at $p < 0.01$.

Results

The SP of the population generally appeared to fall within standard limits or was markedly reduced, reappearing in relation to tremor frequency and the resetting phenomenon due to cortical stimulus. The frequency pattern fell mainly between 5 and 6 Hz, although a small group of 6 patients (20%) showed a 7–8 Hz frequency. The EMG study almost solely pointed to a tremor synchronism between agonist and antagonist muscles. All the data further confirmed that the EMG characteristics of all patients were in accordance with the ET diagnosis.

Throughout the study, treatment with mirtazapine showed a tolerability profile that seemed favourable in most cases, only 3 patients had to stop taking the treatment because of undesirable circumstances (undue drowsiness in 2 cases and excitement in 1 case).

Table 3 Clinical evaluation of essential tremor (ET) before and after 1 month of treatment with mirtazapine (30 mg/daily) (number of patients = 27)

	Before treatment	After treatment	p
Resting tremor	–	–	–
Postural tremor	2.11 ± 0.42[a]	1.19 ± 0.56	< 0.01
Action tremor			
C1: in alternating flexion/extension arm movements	1.41 ± 0.64	0.74 ± 0.71	< 0.01
C2: in reaching a target (index/nose test)	1.56 ± 0.75	0.89 ± 0.58	< 0.01
Orthostatic tremor	–	–	–
Tremor of the head	0.96 ± 1.01	0.48 ± 0.70	< 0.01
Speech	1.07 ± 0.96	0.59 ± 0.69	< 0.01
Writing	1.67 ± 0.68	0.89 ± 0.70	< 0.01
Overall subjective disability	2.15 ± 0.53	1.04 ± 0.65	< 0.01

[a] Values are means ± standard deviation of mean.

Effectiveness of the treatment was analyzed by observing 27 patients who had completed the first month of treatment. Mirtazapine assured good control of tremor symptoms in 23/27 patients (85%). A statistically significant difference was found for these patients when comparing basal and post-treatment evaluations dealing with postural tremor, action tremor, tremor of the head, and for speech and writing (Table 3). Furthermore, overall subjective disability improved significantly for those patients with a great variation between basal and post-treatment assessments (2.17 ± 0.53 vs 1.13 ± 0.73, $p < 0.001$).

The subgroups consisting of those patients who did or did not show a family history for tremor were then compared, but no statistically significant differences were found. A differential analysis was also carried out on subgroups with different tremor frequencies (< 7 Hz and ≥ 7 Hz), but again no differences of statistical relevance were found for treatment efficacy.

Finally, none of the apomorphine-tested patients showed important modifications in their SP, and the pharmacological treatment with mirtazapine did not bring about any substantial variation in their electrophysiological parameters.

Discussion

Our study, an open-label design but with a "blind" observer, suggests that mirtazapine is a valuable drug in assuring effective control of tremor symptoms. Of 27 patients suffering from ET who received at least 1 month of treatment, 85% gained substantial benefit, and the benefit persisted essentially unchanged for 6 months in 75% of the cases and for up to 1 year after starting the treatment in 55% of the cases (15 patients have in fact already completed their first year of treatment).

The patients included in the study had EMG characteristics that were in accordance with the ET diagnosis (Deuschl et al 1987), and the apomorphine test did not determine any remarkable change in their SP compared with what can commonly be observed in patients suffering from the tremor-causing syndrome of Parkinson's disease (Manfredi et al 1998).

During the EMG examination two distinct main tremor frequencies were also detected (5–6 Hz and 7–8 Hz) and a group of patients whose SP was considerably reduced was also identified. These characteristics were not, however, associated with any element that could clinically differentiate the two subgroups and did not seem to be connected to treatment response; mirtazapine was found to be equally effective in both subgroups of selected patients. Similarly, the clinical efficacy of mirtazapine did not appear to be linked to a family history for tremor symptoms.

Our data, therefore, seem to agree with the preliminary observations reported (Pact and Giduz 1999; Gordon et al 2002), which pointed out the clinical efficacy of mirtazapine in those pathological states characterized by tremor, both of the Parkinson's and the essential type, suggesting a specific action of the drug on that symptom.

Tolerability also proved to be good, with a reduced rate of drop-outs. Only 3 out of the 27 patients who completed the trial felt a small sedation/drowsiness during daytime, most noticeable during the first weeks of treatment, but these patients continued the treatment nonetheless. Three patients complained about a slight gain in weight (about 2–3 kg). Only one patient wished to stop taking mirtazapine, notwithstanding the excellent control over tremor, because of a considerable gain in weight. No anomalies were detected either in the hematological or in other biohumoral indexes during the observation phase. Finally, mirtazapine did not alter the electrophysiological parameters throughout the treatment.

For those patients who stopped taking the drug or did not respond to the treatment it must be noted that they were older with more complicated case histories, and sometimes they had received previous treatment (beta-blockers, benzodiazepines, anticholinergics, primidone) that had not given the desired results or had been only partially effective.

The very many co-morbidities (high blood pressure in 40%, dysthymia/anxiety in 26.6%, diabetes in 13.3%), together with the relevant therapies to be undertaken, did

not show interference problems in association with a combined intake of mirtazapine. Depression symptoms of patients suffering from mood disorders also generally improved. Although a quarter of patients were affected by dysthymia/anxiety, they did not show different responses compared with the remaining patients.

Mirtazapine is an antidepressant with noradrenergic and serotoninergic actions; some of the clinical efficacy of the drug may be related to its sedative or anxiolytic effects (especially on the psychogenic component of postural and action tremors), but our impression is that mirtazapine performs its action independently.

In summary, mirtazapine proved to be extremely valuable for treating tremor in patients suffering from ET, with rare side-effects, because of its mono administration, tolerability, and non-interference with any concomitant therapy. The subjective benefit was most evident and lasting for all patients who responded to the treatment (over 80%) and who then wished to continue. Lastly, mirtazapine was effective in all patients afflicted with ET, irrespective of their electrophysiological and/or hereditary characteristics, with unchanged efficacy and of long duration.

New studies, preferably double-blind and placebo-controlled, should be performed on the role of mirtazapine in the treatment of different types of tremor in order to confirm the promising results of our study and of other preliminary studies.

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