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Distigmine and Amitriptyline in the Treatment of Chronic Pain

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Sixty-five patients attending a pain relief clinic were randomly allocated to treatment for 5 weeks with amitriptyline alone, distigmine alone, amitriptyline and distigmine started together, or addition of distigmine to preexisting treatment with amitriptyline. Forty-eight patients successfully completed the trial; the most common cause for withdrawal was dry mouth in the amitriptyline-alone group. Two parameters were measured: Pain intensity was measured at the beginning and end of the treatment, and the saliva flow was measured at the beginning and the end of the treatment. At the end of 5 weeks, treatment with a combination of amitriptyline (75 mg/day) and distigmine (10 mg/day) resulted in a 43% reduction of pain and no subjectively noticeable mouth dryness. Distigmine alone also decreased pain and increased saliva flow, sometimes to the point of discomfort, whereas amitriptyline alone, in this particular series, did not significantly reduce pain and produced unpleasant mouth dryness. The addition of distigmine to preexisting (and ineffective) amitriptyline treatment failed to relieve pain. We therefore conclude that a combination of amitriptyline and distigmine (both given *ab initio*) may be a useful therapy for chronic pain.

Amitriptyline has been in use for the treatment of chronic pain for 15 years[1] and has been found to be particularly valuable in the treatment of neurogenic pains, such as post-herpetic neuralgia.[2,3] Its action in relieving pain appears to be independent of its antidepressant action.[4,7] Schott & Loch[6] reported the successful use of an anticholinesterase (physostigmine) in three cases of neurogenic pain, and Free[4] reported three cases relieved by distigmine. Anticholinesterases are known to cause hypersalivation as well.[8] We therefore decided to undertake a larger trial on the pain-relieving effects of a drug in each of these categories, both singly and in combination. The anticholinesterase chosen was distigmine, because its penetration of the blood-brain barrier is less than that of other drugs of the same type.

MATERIALS AND METHODS

A total of 65 patients attending the Centre for Pain Relief for treatment of a variety of long-standing painful conditions were randomly allocated into three groups. The following figures refer to the numbers completing the trial: (1) nine patients were treated with amitriptyline (50 to 75mg/day in divided doses, starting with 25mg in week one and adding another 25mg in week two and, in some cases, a further 25mg in week three) alone; (2) thirteen patients were treated with distigmine (10mg/day, given as 5mg 30 minutes before breakfast in week one and adding a further 5mg 30 minutes before the last meal of the day) alone; (3) fourteen patients were given a combination of amitriptyline (50 to 75mg/day dosed as in [1]) and distigmine (10mg/day, dosed as in [2]) *ab initio*; and (4) a further 14 patients who had already been taking amitriptyline (50 to 75mg/day) for at least 2 months beforehand were given distigmine (10mg/day, dosed as in [2]) in addition.

The trial period lasted 5 weeks. At the beginning and end of the trial, the resting salivary flow was measured. The patient was sitting in a forward position collecting the saliva in a tube for 10 minutes. At the beginning of the

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Table 1. Patients Taking Amitriptyline Alone

Patient	Age	Sex	Diagnosis	Pain Duration	mL Saliva/10 min		VAS (cm)	
					Before	After	Before	After
JK	53	M	LBP	3yr	9.5	4.5	10.0	10.0
AJ	47	F	LBP	5yr	5.0	2.8	4.8	7.0
WE	32	M	LBP	4yr	5.0	1.5	7.0	5.5
HS	74	M	Burning mouth	8yr	3.0	2.2	5.0	1.6
LB	65	F	AFP	13yr	1.0	0.4	4.5	6.0
GR	73	F	PHN	7mo	2.5	0.9	9.8	9.0
EC	70	F	PHN	9mo	1.0	0.5	9.5	8.0
RD	49	F	LBP	15yr	1.5	0.5	8.5	3.0
RW	42	M	Posttrauma	1yr	9.0	8.0	Not completed	

Mean: 4.2 ± 3.25, 2.4 ± 3.6, 7.4 ± 2.4, 6.3 ± 2.9
Change: −43.2%, $p < 0.001$ −15.2%, NS
Key: AFP = Atypical facial pain, LBP = Low back pain, MS = Painful multiple sclerosis, NS = Not significant, PHN = Post-herpetic neuralgia, Thalamic = Poststroke pain

trial, the patient was familiarized with the visual analog pain scale (VAS)[9] and given a sheet of paper with 35 horizontal 10-cm lines on it, marked NO PAIN at the left-hand end and WORST PAIN EVER at the right. The patient was instructed to mark the VAS at the same time every day according to his/her subjective pain level.

RESULTS

Differences in the resting salivary flow and in experience of pain were found between the groups as a result of the treatment. The results on patients finishing the trials are set out in Tables I to IV.

DISCUSSION

Because of subjective differences in pain evaluation, interpatient comparisons of VAS ratings are not valuable, but the intraindividual percent changes are highly significant.[9] When patients were subjected to the double-tailed t-test, the pain relief at the end of 5 weeks' treatment as measured by the VAS ratings in patients treated by amitriptyline alone (Table 1) and by amitriptyline with the later addition of distigmine (Table 4) is not significant. In patients treated with distigmine alone (Table 2) or amitriptyline and distigmine initiated together (Table 3), on the other hand, the pain relief as shown by VAS ratings is highly significant ($p < 0.001$) in both cases.

Table 2. Patients Treated with Distigmine Alone

Patient	Age	Sex	Diagnosis	Pain Duration	mL Saliva/10 min		VAS (cm)	
					Before	After	Before	After
RR	73	M	Thalamic	2.5 yr	2.5	1.0	8.0	4.5
BN	45	M	LBP	3 yr	5.5	3.5	5.5	4.5
BR	47	M	AFP	2 yr	7.5	7.5	3.0	1.0
GR	51	M	Dysasthesia	2 yr	5.0	7.0	3.0	1.0
MC	75	F	PHN	4 yr	1.0	4.0	5.5	6.0
MN	73	F	PHN	6 yr	1.0	0.75	9.5	5.5
DC	58	M	Thalamic	8 yr	7.0	10.0	8.5	3.0
JJ	30	F	Cervicalgia	3 yr	1.0	1.0	6.5	6.5
BL	30	M	Causalgia	4 yr	5.0	8.0	10.0	8.5
GR	73	F	PHN	8 mo	4.0	4.0	9.5	9.0
GW	62	M	PHN	8 yr	1.0	5.0	5.5	4.0
GM	66	M	Thalamic	2 yr	5.0	9.0	6.0	4.0
JC	47	M	PHN	2.5 yr	5.8	7.0	6.0	3.0

Mean: 3.95 ± 2.4, 5.2 ± 3.1, 6.65 ± 2.3, 4.65 ± 2.4
Change: +31.9% ($p < 0.05$) −30.1% ($p < 0.001$)
Key: AFP = Atypical facial pain, LBP = Low back pain, MS = Painful multiple sclerosis, NS = Not significant, PHN = Post-herpetic neuralgia, Thalamic = Poststroke pain

Table 3. Patients Starting with Amitriptyline and Distigmine Together

Patient	Age	Sex	Diagnosis	Pain Duration	mL Saliva/10 min		VAS (cm)	
					Before	After	Before	After
BN	45	M	LBP	3 yr	5.5	3.5	8.2	2.0
MC	50	F	LBP	2 yr	2.0	2.0	7.0	0.5
JP	36	M	LBP	3 yr	7.5	2.5	8.0	7.0
MH	44	F	LBP	12 yr	8.0	5.3	8.0	6.5
MM	45	F	PHN	1.5 yr	1.0	0.75	4.0	5.0
TR	72	M	PHN	4 yr	0.5	0.75	9.0	9.0
JG	50	F	PHN	1 yr	2.5	1.0	8.5	3.0
MT	53	F	PHN	4 mo	2.5	1.0	8.0	0.5
RS	70	M	Postop	4 mo	7.5	5.0	8.5	4.5
AD	72	M	PHN	2 yr	1.0	1.2	7.0	4.5
JC	66	M	PHN	5 mo	4.0	2.5	8.0	6.5
FW	76	M	LBP	5 yr	4.0	3.0	6.0	6.0
FS	73	F	PHN	2.5 yr	6.0	5.0	8.0	1.0
JB	64	F	LBP	3 yr	3.0	3.0	4.5	1.5

Mean: 3.9 ± 2.6, 2.61 ± 1.6, 7.3 ± 1.5, 4.1 ± 2.7
Change: −33.6%, ($p < 0.001$) −43.8%, ($p < 0.001$)
Key: AFP = Atypical facial pain, LBP = Low back pain, MS = Painful multiple sclerosis, NS = Not significant, PHN = Post-herpetic neuralgia, Thalamic = Poststroke pain

The reason for there being fewer than 15 patients finishing the trial in each group was, of course, noncompliance. The most reduced group was the first (amitriptyline alone); five of the six patients failing to complete the trial specifically stated that they had abandoned the treatment because of dry mouth (see Table 1). All patients were seen at the Centre for Pain Relief after failure to relieve pain in primary care and/or elsewhere. They had all therefore had some form of analgesic medication but without effect. We believe that this aspect of the antecedent history eliminates any major possibility of the results reported here being due to a placebo effect. Other factors militating against the possibility of placebo effect are: (1) no patient reported pain relief (as revealed by the daily VAS score) within a day or two of starting treatment; (2) the pain relief reported by patients in group IV was less than would be expected with placebo alone; and (3) we would not in any event expect placebo pain relief to last 5 weeks—and, in many cases, to go on improving after 5 weeks.

Table 4. Patients on Preexisting Amitriptyline with Distigmine Added

Patient	Age	Sex	Diagnosis	Pain Duration	mL Saliva/10 min		VAS (cm)	
					Before	After	Before	After
SG	67	M	Thalamic	2 yr	0.25	3.0	4.5	5.5
SG	79	M	PHN	1.5 yr	1.0	4.0	6.5	4.5
LM	79	F	PHN	5 yr	0.0	0.25	3.0	3.5
AS	52	F	Thalamic	10 yr	1.0	4.5	8.0	9.0
MO	74	F	MS	38 yr	0.3	1.5	7.0	6.0
EM	25	F	LBP	1 yr	0.5	0.75	6.0	7.0
DA	59	M	Thalamic	1.5 yr	0.0	0.25	8.0	8.0
JG	42	F	LBP	4 yr	0.9	0.9	7.0	7.0
MB	56	M	LBP	6.5 yr	3.5	7.0	7.5	6.0
SL	45	F	LPB (Ca)	1 yr	0.5	1.2	8.5	8.5
ZT	65	F	Thalamic	3 yr	0.9	0.9	8.0	8.0
MP	65	F	Thalamic	5 yr	1.0	1.0	4.0	1.0
GS	84	M	PHN	5 yr	0.0	0.0	4.0	3.0
TB	74	M	PHN	2 yr	1.0	2.9	4.5	2.0

Mean: 0.78 ± 0.9, 2.0 ± 2.0, 6.2 ± 1.8, 5.6 ± 2.5
Change: +159.4%, ($p < 0.001$) −8.7%, NS
Key: AFP = Atypical facial pain, LBP = Low back pain, MS = Painful multiple sclerosis, NS = Not significant, PHN = Post-herpetic neuralgia, Thalamic = Poststroke pain

The group receiving amitriptyline and distigmine (group III) together *ab initio* fared better than the other groups from the point of view of pain relief. Distigmine alone (group II) seemed to be about twice as effective as amitriptyline alone (group I), but amitriptyline plus distigmine was better than distigmine alone by almost an order of magnitude. The real surprise, however, was that the patients already on amitriptyline in whom distigmine was added (group IV) recorded considerably less pain relief than those on amitriptyline monotherapy. However, this group was already deriving little or no benefit from amitriptyline alone and therefore constituted a group that was qualitatively different from group I, in particular, and also, perhaps, from other groups. Importantly, some patients in group I (JK, AJ, LB) did not benefit from treatment by amitriptyline alone, while another (GR) benefited only a very little.

It may be added anecdotally that we have now had the opportunity of watching many of these patients over a longer period and have found that most on combined therapy have improved even further; some on distigmine monotherapy have also improved, while others have made no further progress. Distigmine was stopped in the patients who had previously been on amitriptyline (group IV).

Amitriptyline inhibits the reuptake of both serotonin (5-HT) and noradrenalin (NA) within the central nervous system and in the periphery, thereby facilitating the actions of these transmitters. Although the action on 5-HT reuptake is said to be chiefly responsible for the effect on mood, this is unlikely to be the case so far as pain is concerned. This is because descending serotoninergic systems have been shown to activate inhibitory enkephalinergic interneurones[10] and neurogenic pains, such as post-herpetic neuralgia (PHN) and so-called thalamic syndrome, may be virtually defined by their characteristic resistance to opioid analgesics. Descending NA systems, on the other hand, have a direct inhibitory action on dorsal horn interneurones and do not involve opioid mechanisms. This therefore is more likely to underlie the pain-suppressing effect of tricyclics[11] so far as transmitters are concerned. However, the long time over which the analgesic effect becomes established makes it more likely that the effect is due to changes in receptor density, both centrally and peripherally.

Peripherally, amitriptyline is strongly anticholinergic. The most common effect observed clinically is dry mouth, which is by far the most frequent cause of noncompliance with tricyclic treatment. Anticholinesterases, on the other hand, increase parasympathetic tone and so tend to counteract the peripheral actions of tricyclics. Distigmine had already been used specifically to combat dry mouth in patients being treated with amitriptyline for depression.[3] This is seen in the increased saliva flow recorded in Tables 2 and 4. Interestingly, amitriptyline and distigmine administered together (Table 3) decrease saliva flow, though about 25% less than does amitriptyline alone. None of the patients on distigmine, either alone or in combination with amitriptyline, complained of dry mouth or withdrew from the study because of it.

Study of individual cases within Tables 2 and 4 shows that there is no correlation between pain relief as shown by reduction in the VAS and parasympathomimetic activity as shown by change in saliva flow. Indeed, the patients in Table 4 showed an enormous increase in saliva flow (average 159.4%) and negligible improvement in pain relief, as shown by the VAS.

Distigmine is said to penetrate the blood-brain barrier to only a very minor extent so that its action is almost entirely peripheral. It is generally believed that in neurogenic pains there is instability—frequently hyperactivity—of symphathetic action, as shown by the fact that sympathetic blockade or quanethidine depletion of NA terminals may relieve the pain.[12–14] Distigmine brings about an increase of peripheral parasympathetic tone by inactivation of acetylcholinesterase; it does not increase the activity of cholinergic sympathetic ganglia, because at these sites anticholinesterase (ACh) is dissipated by diffusion rather than by enzyme activity. Furthermore, the exhibition of distigmine over time probably brings about an up-regulation of peripheral acetylcholine receptors, which may explain the enormous increase in salivation observed in group IV.

Table 4 shows that following prolonged unsuccessful treatment with amitriptyline, the addition of distigmine has little if any further pain-relieving effect. Amitriptyline is known to modify adrenergic receptor density, resulting in an up-regulation (increase) of alpha-2 receptors.[15] This might be sufficient to negate the increase in parasympathetic (versus sympathetic) tone brought about by the relatively small doses of distigmine that we have been using; it remains to be seen whether increased doses of distigmine would overcome this obstacle.

There are few adverse drug reactions from distigmine. Glaucoma is mentioned in all literature on anticholinesterases, but the number of reported cases from this cause is very low. Some patients speak of "cobwebs in front of the eyes," but this usually passes and does not herald incipient glaucoma. Its effect on the excitability of the myoneural junction has led to increased nocturnal kicking in two or three of our cases. Because of its tendency to increase secretions, care must be taken with the chesty elderly. Preexisting bronchial or bronchiolar pathology is a contraindication, and at the onset of respiratory symptoms, the drug should be stopped. Any "weakness" of micturition is also a contraindication.

We believe that distigmine has a positive antalgesic

action, particularly in combination with a tricyclic. It is now our practice, for the treatment of burning-and-shooting neurogenic pains such as post-herpetic neuralgia, causalgia, or poststroke ("thalamic") pain, to prescribe a combination of amitriptyline, distigmine, and sodium valproate in doses increasing by weekly steps from 25, 5, and 200 mg respectively to 75, 10, and 600 mg.

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