HUMAN PSYCHOPHARMACOLOGY, VOL. 11, 463–467 (1996)

Thyroxine Augmentation of Fluoxetine Treatment for Resistant Depression in the Elderly: An Open Trial

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Drug resistant depression is a confounding entity. More so in populations of elderly depressives where addition of lithium or antidepressant combinations are possibly hazardous. We present an open-trial of thyroxine in elderly patients diagnosed as suffering from resistant depression. Methods — Thyroxine 50 mcg/day was added to fluoxetine 20 mg/day in patients who did not respond to previous, non-SSRI, antidepressant treatment (6 weeks), nor to an additional 6 weeks of fluoxetine. Subjects — Subjects were diagnosed as suffering from major depression, according to DSM-III-R criteria. All had normal thyroid function tests (TSH and FT_4). There were 15 patients in our series: nine females, six males; mean age 72·1 years (±6·5). Results — Patients depression severity was graded using the Hamilton Depression Rating Scale at baseline (before thyroxine augmentation), and 4 weeks after initiation of treatment. Ten of 15 patients responded to thyroxine augmentation (HDRS < 10), 3/15 showed no improvement of HDRS scores and two dropped out due to adverse effects: diarrhoea and tachycardia. Conclusions — Thyroxine augmentation of fluoxetine is effective in elderly subjects resistant to standard treatment, and is relatively safe.

KEY WORDS — depression; thyroxine; fluoxetine; elderly

INTRODUCTION

The treatment of depression is not always successful. Around 30 per cent of the patients fail to improve with the initial psychopharmacological intervention chosen (Guscott and Grof, 1991). There are currently two widely accepted definitions of 'drug-resistant depression': (a) two successive trials of medications of different categories for adequate dosage and duration (6–8 weeks) (Karasu *et al.*, 1993); and (b) no adequate remission to two successive trials of monontherapy, an old and a new generation antidepressant, given in an adequate dose for a sufficient period of time (4–6 weeks) (Helmchen, 1991).

Several therapeutic strategies have been recommended for the management of resistant depression, regardless of its definition: adjunct lithium therapy (Price *et al.*, 1986), addition of psychostimulants (Wharton *et al.*, 1971), thyroid hormone augmentation (Stein and Avni, 1988), simultaneous use of multiple antidepressant medications (Seth *et al.*, 1992), electroconvulsive therapy (Penney *et al.*, 1990), anticonvulsants (Cullen *et al.*, 1991) and even psychosurgery (Bridges, 1992).

Since resistance to antidepressants is often seen in elderly patients with major depression (Bech, 1993), and because in the elderly, remission rates with tricyclic antidepressants are sometimes less than 50 per cent (Gerson *et al.*, 1988), the problem of drug-resistant depression (DRD) in the elderly needs special attention. This is further compounded by relative and absolute contraindications to some of the therapeutic strategies mentioned above.

An attractive strategy for the management of DRD in elderly patients could be the introduction of thyroid hormones. There are several advantages noted in the literature: (a) side-effects related to thyroid hormones are found to be negligible in most studies (Prange *et al.*, 1969), (b) addition of thyroid hormones to standard doses of antidepressants are generally safe (Tsutsui *et al.*, 1979),

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CCC 0885–6222/96/060463–05

(c) there is no increase in the side-effects of either medication (hormone or antidepressant) with this combination (Goodwin *et al.*, 1982) and (d) the combination does not adversely affect cardiac functioning (Garbutt *et al.*, 1979).

We present a series of elderly depressed patients who did not respond to two antidepressant medications, and therefore thyroxine 50 mcg/day was added to the treatment regime for 4 weeks.

METHODS AND SUBJECTS

Methods

For the purpose present study the following definition of 'drug-resistant-depression' (DRD) was used: major depression was diagnosed according to the criteria of the DSM-III-R (APA, 1987) following a semistructured interview based on the principles of the SADS-L. The Hamilton Depression Rating Scale, (HDRS) score in each patient was above 20 (Paykel, 1990) at the end of 12 weeks of antidepressant treatment. The treatment period consisted of 6 weeks of a tricyclic agent, followed by 6 weeks of fluoxetine. No improvement in CGI during the 12 weeks was noted.

All patients underwent a complete physical and neurological examination prior to drug treatment. The following laboratory tests were undertaken at that time: ESR, CBC, urinalysis, glucose, complete liver and kidney function, thyroid function (FT_4, TSH), EKG. These examinations were also performed at the end of the trial.

Inclusions criteria

(a) Defined as DRD, according to the above-mentioned criteria; (b) age 60 years, or older.

Exclusion criteria

Evidence of (a) pre-existing physical disorder, (b) any disturbance in laboratory examinations, (c) existence of psychotic features, (d) abnormal thyroid function tests before the study and (e) past history of thyroid dysfunction.

Following 12 weeks of antidepressant treatment, thyroxine 50 mcg/day was added to 20 mg/day of fluoxetine. The patients underwent this regimen for 4 consecutive weeks. HDRS was administered at 'baseline' (i.e. after 12 weeks of antidepressant treatment) and after 4 weeks of thyroid-augmentation.

Subjects

There were 15 patients in our series: nine females and six males. All patients signed an informed consent form prior to the study. Mean age was 72·1 years, ($SD = 6{\cdot}5$). The tricyclics used in the first 6 weeks were: mianserin ($N = 9$), 60 mg/day, doxepin ($N = 3$), 125 mg/day and desipramine ($N = 3$), 200 mg/day. Fluoxetine administered in the following 6 weeks, and to which thyroxine was later added, was given in a single morning dose of 20 mg/day. Two patients, (both female), had to discontinue this treatment, one due to diarrhoea, and the other because of the development of severe tachycardia. Thirteen patients, therefore, completed the study.

Statistical analysis

Differences between the HDRS scores and thyroid hormone levels before and after thyroxine augmentation were evaluated by the paired Student *t*-test for dependent samples, for the 13 patients completing the study.

Reduction in HDRS score to less than 10 was defined as a successful outcome (Paykel, 1990). Chi square analysis was employed to evaluate the effects of thyroxine augmentation according to this criterion.

RESULTS

Baseline (before thyroxine augmentation) HDRS mean score was 23·2 (SD = 2·9). The mean score at the end of the treatment period was 14·8 (SD = 4·2). The differences between the two scores, i.e. the effect of thyroxine augmentation, was found to be statistically significant $t = 3{\cdot}61$ $df = 12$ $p < 0{\cdot}01$.

Ten of 15 subjects had HDRS scores of 10 or less, following 4 weeks of thyroxine augmentation, and three demonstrated HDRS scores higher than 17. The effect of thyroid treatment, according to this criterion was also found to be highly significant $X^2 = 9{\cdot}2$, $p < 0{\cdot}01$.

Except for the two patients who had to be excluded from the study, there was no evidence of significant adverse effects, with the addition of thyroxine. Heart rate and blood pressure were not increased, nor were there are notable changes in the patients' EKGs.

Thyroid hormone levels at the beginning of the study were in the normal range, according to our laboratory: $FT_4 = 1{\cdot}1 \pm 0{\cdot}2$ (0·9–1·4) and TSH–$1{\cdot}3 \pm 0{\cdot}4$ (0·6–2·7). There were no significant

changes in the levels of these hormones following thyroxine augmentation ($FT_4 = 1{\cdot}2 \pm 0{\cdot}2$; $TSH = 1{\cdot}1 \pm 0{\cdot}3$).

DISCUSSION

Treatment of depression is considered particularly complicated in the elderly (Gerson *et al.*, 1988). In the first place, depressive symptoms at that age are often equivocal and difficult to diagnose (Lishman, 1978) and may mimic a cognitive, rather than an affective, impairment (Lishman, 1978). In addition, the improvement rates with standard antidepressants are less remarkable in the older age groups (Gerson *et al.*, 1988) and the dosage-adjustment is often complex. There is high co-morbidity, in the elderly, of depression and physical disorders in which tricyclic antidepressants are usually contraindicated, e.g. dementia, cardiovascular disturbances, glaucoma or obstructive uropathies (Helmchen, 1991). In addition, the adverse anticholinergic and orthostatic effects of tricyclics are particularly hazardous in older patients (APA, 1987; Helmchen, 1991).

The treatment of depression in old age calls, therefore, for the constant development of novel strategies. Not only are these patients more resistant to standard antidepressants (Bech, 1993), but some of the treatment strategies employed in DRD are contraindicated in the elderly. The addition of lithium (Price *et al.*, 1986) or psychostimulants (Bridges, 1992) can be associated at that age with the development of confusional states, and the employment of multiple medications is not warranted because of additive adverse effects (APA, 1987; Helmchen, 1991).

Reviewing the relevant literature, we have not found studies on thyroid hormone augmentation of tricyclic antidepressants in the management of DRD in the elderly. Moreover, only a few case reports have actually examined, so far, the antidepressant effect of combining thyroid hormones with SSRIs, e.g. fluoxetine.

Crow *et al.* (1990), describe a case of a 73-year-old male, suffering from major depression, which did not respond to fluoxetine 40 mg daily for 3 months, or to lithium carbonate augmentation for the subsequent 6 weeks. L-Triiodothyronine, 25 mcg/day was added, and within 4 days, the patient showed significant improvement in his depressive symptoms.

Gutpa *et al.* (1991), treated a 30-year-old female, diagnosed as suffering from major depressive disorder, with fluoxetine up to 40 mg/day, for 10 weeks, with no significant change from baseline. Addition of L-triiodithyronine, 25 mcg/day resulted in a dramatic improvement of the depressive symptomatology within 6 days, which persisted throughout the 4-week treatment period.

Jaffe (1992) reports three cases of triiodothyronine potentiation of the antidepressant effect of fluoxetine. In this report the results suggest that T_3 augmentation may be effective with fluoxetine as well as other tricyclic antidepressants.

The present study is the first to evaluate the effect of thyroid augmentation of an SSRI agent in DRD in the elderly, with a fixed dose, controlled open design. DRD was defined with rigorous criteria, i.e. two successive trials of two different antidepressants, given in adequate dosages (either mianserin 60 mg/day, doxepin 125 mg/day, or desipramine 200 md/day, followed by fluoxetine 20 mg/day) for adequate periods of time (6 weeks each) (Helmchen, 1991; Karasu *et al.*, 1993). The level of depression before combined treatment ($HDRS = 23{\cdot}2 \pm 2{\cdot}9$) was in the range of moderate–severe (Paykel, 1990) i.e. we were treating elderly patients with quite severe depression.

The selection of fluoxetine as the medication to which thyroid hormones have been added, as well as its dosage are based on its overall efficacy, tolerance and safety in elderly depressed patients (Karasu *et al.*, 1993). Although most studies have added triiodothyronine to the standard antidepressants, thyroxine is also found to be efficacious in these patients (Tergum *et al.*, 1984). Moreover, Prange (1987) claims that 'on balance, one must guess that thyroxine (T_4) is probably as effective as triiodothyroine (T_3) as a tricyclic-adjunct in depressed patients'. A dose of 100 mcg of T_4 is equivalent to 25 mcg of T_3, the preferred dosage for thyroid augmentation (Prange, 1987). We have decided to use a smaller dosage — 50 mcg/day — because of the lower metabolism rate of thyroxine in elderly patients.

The present study suggests that thyroid hormone augmentation of an SSRI agent could be an efficacious, basically well-tolerated and safe strategy for the treatment of DRD in elderly patients. The few case reports in this field have emphasized the quick remission with this combination, even in severe and prolonged DRD (Crow *et al.*, 1990; Gutpa *et al.*, 1991); similar results have been also reported when adding T_3 to tricyclic antidepressants (Prange, 1987; Stein and Avni, 1988).

Further studies are required to validate these findings. Another important issue relates to the low rate of adverse effects when combining T_4 and fluoxetine, demonstrated both in the present and various other studies (Crow *et al.*, 1990; Gutpa *et al.*, 1991; Jaffe, 1992). This has been generally the case also in the treatment of depression with thyroid hormones and tricyclic antidepressants (Prange *et al.*, 1969; Garbutt *et al.*, 1979; Tsutsui *et al.*, 1979; Goodwin *et al.*, 1982), although the experience with elderly populations is very limited (Stein and Avni, 1988). The low rate of side-effects in the present study, in particular the lack of significant cardiovascular involvement, suggests that thyroid hormones and SSRIs may have a particularly important role in the management of DRD in old age, particularly when bearing in mind that other treatment modalities are often contra-indicated in these patients.

Conclusion

Combining T_4 with fluoxetine in an open, fixed dose design, has been found to be efficacious, well tolerated and safe in elderly patients with drug resistant depression. Controlled double-blind studies are required to validate the results of the present study, and to further evaluate the role of thyroid hormone augmentation in the treatment of DRD in the old age.

Comment

Following the study's termination (and discontinuation of T_4 augmentation), patients were followed at our centre's outpatients clinic. The five patients who either dropped out or did not respond to T_4 augmentation were treated with fluvoxamine ($N = 3$) or moclobemide ($N = 2$); we do not have formal HDS scores for them but impressions of treating psychiatrists were of a gradual improvement over a 3-month period. Of the 10 patients who responded well to the T_4 augmentation, eight were clinically judged to remain in remission at a follow-up visit, 3 months after the trial's termination. Two patients were not available for follow-up.

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