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Triiodothyronine augmentation for the treatment of depression in substance misusers unresponsive to tricyclic antidepressants

利用三碘甲狀腺氨酸強化療法治療對於三環抗抑鬱藥物無效的濫用藥物的病人

We report on two substance misusers with depression resistant to tricyclic antidepressant treatment who responded to triiodothyronine augmentation. The management of resistant depression, augmentation strategies with particular reference to triiodothyronine, and the possible mechanism of action of triiodothyronine are discussed.

本文報告了兩名濫用藥物的病人，他們分別患上抑鬱症。利用三環抗抑鬱藥醫治這兩名患者皆無效，但利用三碘甲狀腺氨酸強化療法卻起了作用。本文討論了對於處理頑固的抑鬱症的方法，特別針對三碘甲狀腺氨酸的強化治療的策略，以及三碘甲狀腺氨酸的作用可能的機制。

Introduction

Depression is a common condition—the National Comorbidity Survey in the US found a lifetime prevalence of 17% for major depression.[1] Annually, approximately 3% of the general population in the UK receive treatment for depression from their general practitioners.[2] Despite the well-established efficacy of antidepressants in the treatment of depression, approximately 30% of patients fail to respond to tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors.[3]

Potentiation of antidepressant effects by L-triiodothyronine (T_3) in tricyclic nonresponders was first reported by Prange et al in 1969.[4] L-triiodothyronine augmentation, however, has remained relatively underused locally and in other countries. A survey in the UK found that the T_3 augmentation strategy has rarely been used among resistant depression.[5] A similar scenario exists locally, as revealed from the questionnaire survey among Hong Kong psychiatric trainees.[6] One of the reasons for the underutilisation of T_3 augmentation is the lack of experience among psychiatrists. Thus, while reports in the literature have shown the usefulness of the strategy, it has rarely been applied in clinical practice.

No reports of T_3 augmentation were found in the *Hong Kong Medical Journal* or the *Hong Kong Journal of Psychiatry* during the past 10 years. We report here two cases of depression resistant to TCA treatment—both patients were substance misusers who responded to T_3 augmentation.

Key words:
Antidepressive agents, tricyclic;
Depression;
Triiodothyronine, drug effects;
Triiodothyronine, therapeutic use

關鍵詞：
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Case reports

Case 1

A 22-year-old Chinese single unemployed woman first presented in December 1995 with visual and auditory hallucination for 4 months. Her mood was not depressed at that time. She drank a bottle of cough mixture a day and had been dependent on it since she was 17 years old. She also used cannabis and benzodiazepines occasionally. She was diagnosed with drug-induced psychosis. She was prescribed thioridazine 50 mg/d for 3 months and her psychotic symptoms gradually subsided.

The patient was admitted to Queen Mary Hospital in September 1998 when she presented with restlessness, agitation, disorientation, and irrelevant speech for 2 days. She had been misusing methamphetamine intermittently since July 1997, when she gradually stopped using cough mixture. Urine toxicology on admission showed amphetamine and a diagnosis of amphetamine intoxication was made. She made a spontaneous recovery 3 days after admission, but, she became severely depressed with frequent weeping episodes, loss of interest, insomnia, decreased appetite, sense of worthlessness, and guilt feelings with self-blame. Amitriptyline was started at an increased dose of 200 mg/d for 8 weeks. She failed to respond, however, and haloperidol up to 8 mg/d was added for 2 weeks but was stopped when there was no sign of significant improvement. Investigation results were unremarkable except for a persistent low free thyroxine (T_4) of 0.9 pmol/L (normal range, 10-36 pmol/L) with normal thyroid-stimulating hormone (TSH) level and elevated anti-thyroglobulin. She was clinically euthyroid. While amitriptyline was maintained at 200 mg/d, T_3 augmentation was started with an initial dose of 20 μg for 5 weeks, and then increased to 40 μg. Her mood improved after 1 week of T_3 augmentation and she experienced complete remission 6 weeks later. At discharge, she was cheerful with no further depressive symptoms. L-triiodothyronine was maintained for another 2 months before tapering of the dose.

Case 2

An 18-year-old Chinese single unemployed man had been a polysubstance misuser since the age of 13 years. He first experimented with cannabis, then quickly graduated to daily use of methamphetamine by fume inhalation. At the age of 15 years, he stopped using methamphetamine and started taking heroin. He became dependent on heroin and used up to one tablet per day.

The diagnosis of depression was first made at the age of 16 years when he presented with loss of interest, decreased energy, loss of confidence, poor concentration, recurrent suicidal ideas, insomnia, and loss of appetite for the previous 2 months. At that time he was misusing heroin only and the pattern of its use apparently had no relationship to his depressed mood. He was admitted twice for detoxification and treatment of depression in November 1998 and June 1999. His depression responded partially to dothiepin 150 mg/d and he had mild depressive symptoms in between treatment episodes. His drug compliance was good.

His mood deteriorated again in September 1999. This mood change was apparently precipitated by the tense family relationship he experienced as a result of his continued use of heroin. An attempt was made to further increase the dose of dothiepin but he could not tolerate the feelings of sedation and dizziness. After detoxification with methadone replacement, he remained depressed with similar symptoms to those he previously experienced. All investigations including thyroid function test were normal. Subsequently, T_3 augmentation was started with T_3 20 μg/d and increasing to 40 μg/d for 10 days. The dothiepin dose remained at 150 mg/d. Some improvement in mood was noted 3 days after T_3 augmentation. After 2 weeks, he had no more episodes of crying and his energy and interest recovered. He participated actively in ward activities and began to plan his future. L-triiodothyronine was reduced 2 months later and he remained euthymic and abstained from heroin.

Discussion

When patients do not respond to an adequate trial of a TCA, drug compliance should be checked, the diagnosis reviewed, and any perpetuating factors, such as important stressors should not be overlooked. For the true nonresponders, treatment options include switching to another antidepressant, electroconvulsive therapy, or using an augmentation strategy. Whether to switch antidepressants or to augment depends on the severity of illness and the side-effects of the current medication. Switching to another antidepressant has the advantage of keeping the treatment simple and thus helps to improve compliance. Augmentation often produces a more rapid onset of action, however. This approach may also help to improve the initial response of the first agent or add other beneficial effects to the original regimen.[7]

Of all the augmentation strategies, lithium augmentation has received the most attention. There has been increasing evidence of the effectiveness of

T_3 augmentation, however. In 1982, Goodwin et al[8] performed the first double-blind study reporting the efficacy of T_3 in converting TCA nonresponders to responders. A recent meta-analysis has reported that depressed patients resistant to treatment given T_3 augmentation were two-fold more likely to respond than non-augmented controls.[9] Systematic comparison of T_3 and lithium found that each was effective in approximately two thirds of TCA nonresponders. It remains impossible, however, to predict which patients will respond better to T_3 or lithium augmentation. Joffe[10] reported that patients who did respond to the addition of T_3 were less likely to benefit from adjunctive lithium and vice versa.

The usual dose of T_3 in augmentation therapy is 25 μg/d to 50 μg/d. A starting dose of 20 μg increasing to 40 μg was given to the patients in this study. Initial improvement in mood is usually apparent within several days. Goodwin et al[8] reported that there was improvement in all aspects of the depressive syndrome within 1 to 3 days. For the two patients in this study, initial responses were noted after 3 and 7 days. An adequate trial of T_3 augmentation should last for 7 to 14 days to reach its full effect. If T_3 augmentation is effective, most studies recommend a maintenance period of 2 months before gradually reducing the dose at the rate of 10 μg every 3 to 7 days.

L-triiodothyronine augmentation therapy should not be used in the presence of endocrine disorders such as hyperthyroidism, uncorrected adrenal insufficiency, and phaeochromocytoma. It is also contraindicated for patients with cardiac disease, angina, acute myocardial infarction, or hypertension. Adverse reactions are uncommon if daily doses do not exceed 50 μg. The two patients reported here did not have any side-effects. While receiving treatment, patients should be monitored for signs and symptoms of thyrotoxicosis.

The two cases illustrated here show a common feature. Both subjects were substance misusers and yet they responded to T_3 augmentation. This suggests that T_3 augmentation can be helpful in resistant depression regardless of the aetiology of the illness. We are not aware of any study specifically conducted on the efficacy of T_3 augmentation among substance misusers. Mood disturbances, in particular depression, however, are common among substance misusers, especially for those who misuse stimulants such as methamphetamine or cocaine. The two patients reported here had a history of methamphetamine misuse. Although the psychiatric symptomatology of most substance misusers tends to fluctuate over time, the two patients were observed to have persistent depression in an in-patient setting, and the depressive symptoms mitigated with T_3 augmentation. The aetiology of depression in substance misusers is complicated since both psychological reactions and physical consequences of illicit drug use may be important. Poor social support, family relationship problems, unemployment, delinquent history, and personality problems are common in substance misusers, as shown for the two reported patients. As a result, depression in substance misusers demands a diverse and aggressive treatment approach. Persistent depression is likely to create difficulties for rehabilitation among drug misusers. Although this report focuses on the drug treatment of these patients, psychosocial approaches should not be overlooked.

The exact mechanism of action of T_3 augmentation remains largely unknown. In depressed patients, the circulating plasma levels of free T_4 appear to be normal, but levels of free T_3 may be decreased. Approximately one third of depressed patients show blunting of the TSH response to thyrotropin releasing hormone. Approximately 15% of depressed patients have elevated basal TSH levels, probably indicating subclinical hypothyroidism, and thyroid autoantibodies are found in a similar percentage of patients.[11] Thyroid abnormalities are found at a higher frequency among TCA nonresponders and this may link with the underlying mechanism of T_3 augmentation.

In most case reports, patients had normal thyroid function, as in our second case. There seems to be no relationship between thyroid state and the efficacy of T_3 augmentation. In the first case, the patient had sick euthyroid syndrome, which is sometimes seen in depressed patients. In this condition, peripheral deiodination of T_4 to T_3 is reduced, although the TSH level is normal.

One proposed mechanism of T_3 augmentation is that T_3 may raise peripheral thyroid hormone concentrations in patients with covert or borderline hypothyroidism. Other authorities believe that there is no difference in the thyroid state of the responders and nonresponders to T_3 augmentation.[12] L-triiodothyronine may act in euthyroid patients through augmentation of the β-adrenergic system.[13] Alternatively, T_3 may also affect thyroid utilisation and local neuronal deiodination in the brain.

Conclusion

L-triiodothyronine augmentation is effective for some TCA nonresponders and the evidence from the

two patients reported here seem to suggest that T_3 augmentation works equally well among substance misusers. It should be remembered, however, that this report consists of only two patients. Although the authors are impressed with the clinical improvement, there is no standardised measure for these changes. Nevertheless, we believed this treatment strategy should be used more often in local practice.

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