Minimizing the cognitive effects of lithium therapy and electroconvulsive therapy using thyroid hormone

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Abstract
Although electroconvulsive therapy (ECT) and lithium are effective treatments for mood disorders, they are both associated with cognitive side-effects that reduce patient compliance and satisfaction. Because both ECT and lithium have significant impact on the hypothalamic–pituitary–thyroid (HPT) axis, at least some of these side-effects may be associated with alterations in HPT activity. There is evidence that cognitive deficits in patients with bipolar disorder taking lithium are related to diminished thyroid status, but not to serum lithium level. A preliminary study showed that adjunctive use of thyroid hormone significantly improves cognitive functioning in patients taking lithium. An animal study and two double-blind, placebo-controlled clinical studies examining the adjunctive use of thyroid hormone (T3) and ECT have confirmed that T3 significantly protects against ECT-related memory impairment compared to placebo. Taken as a whole, this research suggests that adjunctive use of thyroid hormone has the potential to reduce cognitive side-effects of these important psychiatric treatments.

Introduction
Lithium and electroconvulsive therapy (ECT) are very effective therapies for the treatment of mood disorders. However, both are associated with potential cognitive side-effects that can impact patient satisfaction with the treatments, as well as reduce treatment tolerability. There is considerable evidence that these cognitive effects are associated with changes in the hypothalamic–pituitary–thyroid (HPT) axis. This paper will briefly discuss the relationship between the HPT axis and cognitive functioning, highlighting the neurobehavioural effects of overt hyper- and hypothyroidism as well as the cognitive and behavioural implications of subclinical hypothyroidism. Specific cognitive side-effects of both lithium and ECT will be presented, as well as the impact of these treatments on the HPT axis. A lithium–thyroid interactive hypothesis will be described, along with supporting data. We will summarize the results of several studies conducted by our group demonstrating the usefulness of adjunctive thyroid hormone administration in reducing the cognitive side-effects of ECT. We will also present unconfirmed evidence that thyroid hormone can potentially accelerate the antidepressant effect of ECT. Finally, future research directions on the interaction between ECT and lithium and the HPT axis will be discussed.

Relationship between the HPT axis and cognitive functioning
It is widely believed that overt thyroid dysfunction can lead to significant neuropsychological impairments and secondary psychiatric conditions (Stern and Prange, 1995). In this section, we will briefly discuss the cognitive changes associated with alterations of the HPT axis as well as recent functional neuroimaging evidence of specific changes in the central nervous system associated with thyroid dysfunction. Results of a recent study using exogenous T3 to enhance cognitive and emotional functioning will also be reviewed.

Overt hyperthyroidism
There is considerable evidence that hyperthyroidism (most commonly caused by Graves’ disease) is associated
with a variety of cognitive difficulties including impaired problem-solving, reaction time, visual–motor coordination, concentration, and memory (e.g. Stern et al., 1990; Trzepacz et al., 1988; Whybrow et al., 1969). These difficulties clearly can occur during thyrotoxicosis, though their persistence following chemical euthyroidism (either with anti-thyroid medication or radioactive thyroid ablation) is less certain. To further understand the significance of cognitive difficulties associated with hyperthyroidism found throughout the course of diagnosis and treatment, our group (Stern et al., 1996) conducted a mail survey of members of the National Graves Disease Foundation to examine treatment factors and neuropsychiatric complaints of 137 individuals diagnosed with Graves’ disease. Patients were asked to retrospectively rate their cognitive functioning in four domains (i.e. memory, attention, planning, productivity) 2 years prior to hyperthyroid symptoms, while hyperthyroid, and at the time of the survey. Results revealed significantly worse ratings of cognitive functioning for the hyperthyroid period compared to premorbid levels. Surprisingly, patient ratings of current functioning, though better than when they were hyperthyroid, were significantly worse than premorbid ratings. The majority of the respondents also included subjective comments describing the distressing nature of their neuropsychiatric complaints. A recent Dutch survey replicated these findings, revealing continued emotional and cognitive complaints even after patients with Graves’ disease had been euthyroid for 1 year or more (Fahrenfort et al., In Press).

Taken together, results from objective neuropsychological studies of Graves’ disease and the survey studies suggest that executive functioning (controlled by the frontal lobes and associated cortical–subcortical circuits; Stern and Prohaska, 1996) may be particularly affected in Graves’ disease. Further evidence comes from a preliminary study using magnetic resonance spectroscopy that revealed reductions in concentrations of choline-containing compounds in the right prefrontal region of thyrotoxic patients with Graves’ disease compared to euthyroid controls (Bhatara et al., 1998). Follow-up imaging once patients were chemically euthyroid showed significant increases in these compounds compared to hyperthyroid levels, though only half of the original sample was examined.

In a recent study, our group (Tremont et al., 1999) compared the neuropsychological performance of 20 thyrotoxic patients with Graves’ disease to age-, gender-, and education-matched healthy controls on the Rey–Osterrieth Complex Figure (ROCF), a measure of visuospatial skills, visual memory, and executive functioning. Patients were carefully screened to rule out other conditions that could affect CNS functioning. Results showed that, compared to the performance of healthy controls, Graves’ patients performed significantly worse on measures sensitive to executive functioning, including planning, vertical and horizontal expansion of the design, and a score involving attention to details. No significant differences were found in immediate or delayed retention of figures, arguing against significant memory problems. Comprehensive neuropsychological evaluation on a subset of hyperthyroid patients revealed that the only significant difference between patients and healthy controls was on a complex visuospatial conceptualization test (i.e. Raven’s Standard Progressive Matrices), a measure sensitive to executive dysfunction.

Overall, research into the CNS consequences of Graves’ hyperthyroidism implicates frontal systems dysfunction. It is not entirely clear whether these impairments represent the direct CNS effects of the autoimmune disorder or the indirect effects of altered thyroid hormone economy in the brain. Future research into the associations between neurobehavioural symptoms and underlying CNS functioning may more clearly address this issue. To further understand this relationship, our group is currently investigating cerebral perfusion patterns using SPECT imaging and associated neuropsychological performance in patients with Graves’ disease both when thyrotoxic and when chemically euthyroid following iodine-131 treatment.

**Overt hypothyroidism**

Overt hypothyroidism is associated with physical signs and symptoms such as excessive fatigue, cold intolerance, dry skin, and weight loss. In addition to these physical symptoms, patients with severe hypothyroidism can often present with problems resembling an early dementia, frequently complicating differential diagnosis (Haupt and Kurz, 1993; Nemeroff, 1989). Data from case reports and uncontrolled research have suggested mental slowing and long response latencies, reduced concentration, and memory complaints in hypothyroid patients (Hall, 1983). Controlled studies of hypothyroid patients have implicated impaired executive functioning and reduced speed of processing as the most significant areas of deficit (Denicoff et al., 1990; Whybrow et al., 1969). As seen in the hyperthyroidism literature, these findings suggest that the frontal systems (i.e. frontal lobe and subcortical–cortical connections) may be particularly affected by hypothyroidism. Neuroanatomical confirmation of this hypothesis is provided by recent evidence that hypothyroid patients exhibit decreased cerebral metabolism (as measured by magnetic resonance spectroscopy; MRS) in the frontal lobes which returns to normal levels following
thyroidism appear reversible with appropriate treatment. Animal studies using MRS have found similar results (Chapa et al., 1995). In most cases, hypothyroid patients will show rapid improvements in cognitive functioning following thyroid replacement therapy. However, at least one study has demonstrated persistent neuropsychological deficits even after initiation of thyroid hormone replacement therapy, possibly relating to neuronal death (Whybrow et al., 1969).

Subclinical hypothyroidism

Subclinical hypothyroidism is defined as normal levels of circulating thyroxine (T4) and triiodothyronine (T3) in the presence of elevated thyrotropin (TSH), and is much more common than overt hypothyroidism; the prevalence of subclinical hypothyroidism ranges from 6 to 8% in adult women, 3% in adult men, and up to 15% in adults over the age of 60 (Bemben et al., 1994; Tunbridge et al., 1977). Subclinical hypothyroidism can be associated with neurobehavioural symptoms including anergia, malaise, and abulia as well as deficits in selective attention and new learning (Haggerty et al., 1991; Nemeroff, 1989). Patients with subclinical hypothyroidism appear to have an increased lifetime prevalence of depression compared to euthyroid controls (Haggerty et al., 1993). Subclinical hypothyroidism is also commonly found among patients with rapid-cycling bipolar disorder, especially in women (Goldman, 1992). Both overt and subclinical hypothyroidism also occur in significant numbers of patients treated with lithium (Joffe et al., 1988; Salata and Klein, 1987; Shopsin and Gershon, 1973), which will later be discussed in more detail.

Both human and rat studies demonstrated that mild states of hypothyroidism can result in significant neuropsychological or behavioural difficulties (Dratman et al., 1983; Whybrow et al., 1972). Our group (Haggerty et al., 1991) compared the neuropsychological functioning of women with subclinical hypothyroidism to women who were euthyroid. Results showed that hypothyroid patients tended to perform worse than euthyroid patients on measures of verbal and visuospatial recall, as well as on selective attention. Recently, Berry et al. (1997) found that subclinically hypothyroid women did not significantly differ from euthyroid controls on measures of working memory. However, multiple regression analysis revealed that measures of thyroid status (i.e. TSH, FTI) accounted for a significant amount of the variance in verbal working memory, again implicating dysfunction of the frontal systems.

Most research evidence suggests that neuropsychological impairments associated with subclinical hypothyroidism appear reversible with appropriate treatment. Haggerty et al. (1986) presented two cases of patients with subclinical hypothyroidism and associated neuropsychological deficits who showed partial improvement in response to treatment with levothyroxine and psychiatric medications. In a double-blind, cross-over study, Nystrom et al. (1988) administered tests of information processing speed, immediate visual recall, and simple reaction time to 20 women with subclinical hypothyroidism. Results indicated that 25% of patients demonstrated significant improvement on at least two of the neuropsychological tasks following 6 months of treatment with 150 µg levothyroxine. In a similar study, Monzani et al. (1993) compared the neuropsychological performance of 14 patients with subclinical hypothyroidism to 50 controls. At baseline, subclinically hypothyroid patients performed worse on measures of attentional capacity, mental control, and immediate verbal and visual recall than controls. After 6 months of treatment with 100–150 µg levothyroxine, subclinically hypothyroid patients exhibited improvement in immediate verbal and visual recall, with other areas showing no change. Baldini et al. (1997) also found that subclinically hypothyroid patients showed significantly worse memory performance compared to euthyroid controls that significantly improved following levothyroxine treatment. In contrast, Jæscke et al. (1996) randomly assigned 37 subclinically hypothyroid patients (aged 55 or older) to either levothyroxine replacement therapy or placebo and examined their emotional and cognitive functioning. After 6 months of treatment, the only significant finding was that the thyroid replacement group demonstrated statistically significant improvement in memory functioning compared to those patients taking placebo, though the authors suggested that this finding was not clinically significant. They concluded that treatment may not be necessarily indicated in older adults with subclinical hypothyroidism.

Overall, subclinical hypothyroidism appears to be associated with neuropsychological deficits, especially in attention, verbal and visual memory, and reaction time. These impairments appear to be at least partially reversible with thyroid hormone replacement treatment, except there may be less of a response with increasing age. As is the case with overt hypothyroidism, duration of untreated illness may be associated with permanent, residual neuropsychological deficits, though to date this has not been formally studied.

Euthyroid state and cognitive functioning

The relationship between thyroid hormone levels and cognitive functioning has also been examined in healthy, euthyroid individuals. Prinz et al. (1999) administered a
number of intellectual and neuropsychological measures to 44 healthy, euthyroid older males. Their results showed that total T4 and free T4 exhibited significant positive relationships with measures of overall cognitive measures, though total T3 and T3 uptake were not related to any of the cognitive measures. These findings suggest that variations of thyroid hormone levels within the normal range can be related to cognitive functioning.

**T3 and T4**

Recently, there has been some interest in whether triiodothyronine (T3) enhances the effect of thyroxine (T4) replacement therapy for the treatment of hypothyroidism. The thyroid gland synthesizes and releases both T3 and T4, with approx. 80% of serum T3 produced through deiodination of T4 and 20% produced by the thyroid gland (Leonard and Koehrle, 1996). T3 is considered to be the active form of thyroid hormone, with T4 serving as a prohormone for the active T3. These thyroid hormones affect all tissues of the body, though the central nervous system may be most sensitive. Typical treatment for hypothyroidism is T4 replacement therapy, though there is some evidence that not all hypothyroid patients on T4 replacement therapy feel completely back to their premorbid level of emotional and cognitive functioning (Carr et al., 1988).

Escobar-Morreale et al. (1996) found that in thyroidectomized rats, large plasma concentrations of T4 were required to normalize T3 and TSH levels. In a controlled study, they demonstrated that the use of T4 and T3 (generally given in proportion to the amount naturally secreted by the thyroid) in rats resulted in euthyroidism in all tissues, without resulting in supraphysiologic concentrations of T4. In a recent double-blind, cross-over study, Bunevicius et al. (1999) examined the emotional, cognitive, and physiologic functioning of 33 patients with hypothyroidism (secondary to near or total thyroidectomy) who received treatment with standard T4 replacement therapy vs. T4 plus T3 treatment. Results showed that following treatment with the adjunctive T3, patients reported significantly better mood, physical status, and cognitive performance (i.e. mental flexibility, attention) compared to functioning after treatment with T4 alone. The majority of patients also reported a higher level of satisfaction with the combined treatment compared to the standard T4 therapy. These findings suggest that exogenous T3 may play an important role in normalizing thyroid hormone levels in tissues throughout the body, and the brain in particular, as well as provide further support for the use of T3 as adjunctive therapy to psychiatric treatments known to affect the HPT axis.

As can be seen in the literature on neurobehavioural effects of thyroid disease, even minor alterations in the HPT axis can result in significant cognitive and behavioural changes that impact daily functioning. In turn, effective treatment of these conditions seems to result in marked improvement in cognition, mood, and quality of life. In the following sections, we will discuss how common psychiatric treatments can alter the HPT axis, thereby producing symptoms impacting effectiveness and satisfaction with the these therapies.

**Lithium and thyroid hormone**

Lithium is a highly effective medication used for the treatment of bipolar disorder and is frequently used for long-term management of patients with this disorder. However, a significant percentage of patients discontinue treatment against the advice of their treating physicians (Cochran, 1986; Jamison et al., 1979). Adverse side-effects are the most common reason for treatment non-compliance. For example, among patients with bipolar disorder and substance abuse, significantly greater non-compliance due to adverse side-effects was reported with lithium therapy compared to valproic acid treatment (Weiss et al., 1998). In another study, 43% of patients taking lithium experienced physical side-effects such as weight gain, dry mouth, excess thirst, diarrhoea, frequent urination, tremor, drowsiness, indigestion, and constipation (McCreadie and Morrison, 1985). Up to 50% of patients taking lithium also report neuropsychological complaints, including significant memory and concentration problems that impact day-to-day functioning (Gitlin et al., 1989). In this section, we will review the literature on the neuropsychological side-effects of lithium, discuss the effects of lithium on the HPT axis, and highlight research on the interaction between lithium and thyroid functioning.

**Cognitive side-effects of lithium**

Research into the neuropsychological effects of lithium was initially directed at understanding acute effects of the drug in healthy volunteers who reported frequent complaints of memory problems, impaired concentration, confusion, decreased mental clarity, lethargy, and fatigue (Judd, 1979). Similar side-effects were described by psychiatric patients taking lithium, again including memory loss, difficulty learning new information, lethargy, and slowed thinking (Bajor, 1977; Kocsis et al., 1987). Results from studies using objective neuropsychological measures to evaluate patients taking lithium are less clear, possibly because not all patients experience neuropsychological
side-effects. In a comprehensive review of the literature, Prohaska et al. (1995b) identified a general pattern of neuropsychological deficits in some patients taking lithium. The most pronounced effect of lithium appears to be an overall slowing that impacts performance on simple motor, psychomotor, and complex information-processing speed tasks. Other less robust findings in patients taking lithium include increased susceptibility to interference on memory tasks and less efficient transfer of information from short-term to long-term memory. Prohaska et al. (1995b) suggest that the neuropsychological side-effects may be mediated by disruption of thyroid functioning.

Relationship between lithium and the HPT axis

Of all psychotropic medications, lithium has the greatest impact on thyroid functioning. In a majority of patients taking lithium, acute thyroid effects include transient reductions in T4 and T3 and an associated increase in TSH (Shopsin et al., 1974; Wilson and Jefferson, 1985). Increased secretion of TSH typically results in increased production of thyroid hormone, thereby maintaining thyroid homeostasis (Prange et al., 1987). However, thyroid homeostasis does not appear to depend solely on TSH secretion, but rather may be affected by previous thyroid pathology and individual differences in lithium concentrations in the thyroid gland, as well as age and gender. Some patients taking lithium also show a decreased degradation rate of thyroid hormones in the periphery, as well as partial inhibition of thyroid uptake of iodine (Cooper and Simpson, 1974).

Lithium’s effect on the HPT axis involves significant inhibition of thyroid synthesis and metabolism. Specific mechanisms include inhibition of iodine uptake, iodination of tyrosine, release of T3 and T4, peripheral metabolism of thyroid hormones, and stimulatory effects of TSH on the thyroid gland (Beren and Wolff, 1975). In addition to these somewhat indirect effects of lithium on the HPT axis, high concentrations of lithium have been found in the thyroid gland of patients taking the drug, reflecting up to 5 times the concentrations found in the blood stream (Beren et al., 1970; Salata and Klein, 1987). High lithium concentrations replace iodine in the thyroid gland, resulting in reduced production, storage, and release of thyroid hormones (Jefferson et al., 1987). There is also evidence that lithium can inhibit adenylate cyclase which is an important factor in thyroid hormone secretion (Salata and Klein, 1987), as well as potentially reduce tissue deiodination of T4 to T3 (Lazarus, 1986). Recent evidence indicates that lithium can affect gene expression on thyroid hormone receptor isoforms (Hahn et al., 1999).

Lithium has significant antithyroid effects similar to antithyroid medications (e.g. propylthiouracil) and iodine-131. In fact, there is evidence that lithium used in conjunction with iodine-131 results in more rapid and complete euthyroidism and reduction in goitre size in patients with Graves’ hyperthyroidism compared to iodine-131 alone (Bogazzi et al., 1999). Overt hypothyroidism in patients taking lithium has been reported in approx. 5–15% of patients, typically becoming apparent within the first 4 years of lithium therapy. However, there are also reports of overt hypothyroidism developing at later points in treatment (Vincent et al., 1993; Yassa et al., 1988). There is evidence of a relationship between overt hypothyroidism and serum lithium level (Tellian and Rueda-Vasquez, 1993), and there are obvious thyroid effects in patients with lithium toxicity (Lazarus, 1986). A more frequent occurrence among patients taking lithium is subclinical hypothyroidism which may occur in 30–39% of patients (Deodhar et al., 1999; Shopsin and Gershon, 1973). In the following section, we will discuss the thyroid–lithium interaction hypothesis that may partially explain the cognitive side-effects of the drug.

Thyroid–lithium interactive hypothesis

Prohaska et al. (1995b) posited that at least some of the neuropsychological side-effects of lithium are a result of lithium’s impact on thyroid functioning. Their hypothesis is based on the research literature examining the neuropsychological side-effects of lithium, the significant antithyroid properties of lithium, and the neuropsychological consequences of even minor alterations in thyroid functioning. There is some research support for the notion that thyroid dysfunction mediates the relationship between lithium and neuropsychological deficits. In patients on long-term lithium maintenance, motor speed and information-processing speed have been shown to be inversely correlated with TSH levels, and complaints of lethargy and cognitive dysfunction were found to be positively correlated with T4 and inversely correlated with T3 (Kocsis et al., 1987). In these same patients, serum lithium levels and physical and cognitive side-effects were unrelated, suggesting that cognitive difficulties were most associated with changes in thyroid functioning. Similar relationships between T4 and subjective reports of lethargy and cognitive impairment have also been found among lithium-treated patients with subclinical hypothyroidism, consistent with reduced T4 to T3 conversion (Hatterer et al., 1988). Bauer et al. (1990) found that patients with bipolar illness and thyroid dysfunction experience more rapid-cycling courses and often do not respond to lithium therapy compared to individuals...
without thyroid dysfunction. In addition, patients with rapid-cycling bipolar disorder appear to respond better to lithium plus thyroid hormone than lithium alone (Bauer and Whybrow, 1990).

To assess the validity of the lithium–thyroid interactive hypothesis, our group (Prohaska et al., 1996) compared the neuropsychological functioning of individuals on long-term lithium therapy with evidence of subclinical hypothyroidism to those with normal thyroid status. Participants included psychiatric outpatients who were between the ages of 20 and 50, had no history of cardiovascular disease or hypertension, had stable emotional states (based on rating scales), had lithium levels in the therapeutic range, and were on lithium maintenance therapy for at least 6 months. Exclusion criteria included overt thyroid disease, pronounced intellectual impairment, previous head injury, a rapid-cycling course, ECT within the previous 2 years, significant substance abuse, or current antithyroid, anticonvulsant, or antidepressant/neuroleptic medications (with anticholinergic properties). Subclinical hypothyroidism (Sch) was found in 8 subjects as indicated by a TSH level greater than 3.9 µU/ml, and 8 subjects were deemed euthyroid (Euth), with TSH levels between 2.0 and 3.0 µU/ml. A neuropsychological assessment battery consisting of measures of attention, executive functioning, information-processing speed, motor speed and dexterity, psychomotor speed, and memory was administered.

Results of the Prohaska et al. (1996) study showed that Sch subjects performed worse on all neuropsychological measures compared to Euth subjects, though scores on verbal learning and memory tasks were the only variables to reach statistical significance. Sch subjects learned significantly fewer words across five trial presentations, recalled fewer words following interference, and correctly identified fewer words in a recognition format after a 20-min delay than Euth subjects. Performance on these verbal learning and memory tasks was significantly related to TSH level (i.e. the higher the TSH, the worse the memory functioning). In contrast, correlations between these memory tasks and serum lithium levels were not significant, replicating the earlier work by Kocsis et al., (1987).

To further examine the lithium–thyroid interactive hypothesis, Prohaska et al. (1995a) investigated the neuropsychological functioning of 8 subclinically hypothyroid (Sch) and 8 euthyroid (Euth) psychiatric outpatients undergoing lithium maintenance therapy before and after T3 treatment in a double-blind, cross-over study. Patients were randomly assigned to either 4 wk of T3 (liothyronine) treatment (25 µg for 2 wk and 50 µg for 2 wk) or a placebo group. After 4 wk treatment, patients underwent 4 wk of the alternative treatment they had not previously received (i.e. either T3 or placebo). Significant improvements were seen on measures of information-processing speed and motor speed in both Sch and Euth patients receiving 4 wk of thyroid hormone, suggesting the effect was independent of initial thyroid status. These results provide preliminary support for the use of thyroid hormone to reduce some of the cognitive side-effects of lithium therapy. Replication of these findings in a larger sample could have major impact on the clinical treatment of bipolar disorder as well as potentially improve lithium compliance. Our group is currently conducting a larger scale, double-blind, placebo-controlled study examining the effect of adjunctive thyroid hormone in patients with bipolar disorder taking lithium.

**Relationship between ECT and thyroid hormone**

Electroconvulsive therapy (ECT) is frequently used in individuals who do not respond to antidepressant medication, or who experience severe, disabling symptoms (Fink, 1987). Despite its demonstrated effectiveness and safety, ECT is often reserved as a final intervention option due to the possible adverse cognitive effects, including temporary confusion and memory disturbance (see Calev, 1994, for review). Cognitive side-effects are important factors which limit the use of ECT, negatively affecting patient satisfaction with the procedure, and continue the negative stigma associated with this effective treatment modality. Even though the cognitive effects of ECT resolve rather quickly, up to 75% of patients receiving ECT report that memory loss is the worst side-effect (Duborsky, 1995). The use of adjunctive medications to potentially reduce these cognitive effects has shown little benefit (Krueger et al., 1992). Similarly, altering the ECT procedure to reduce memory effects typically results in reduced clinical efficacy (Sackeim et al., 1993). We will discuss the effect of ECT on the HPT axis, review the literature on adjunctive thyroid hormone and ECT, present the results of our recent controlled trial using thyroid hormone in patients receiving ECT, and highlight some of the possible mechanisms of action.

**Impact of ECT on the HPT axis**

The therapeutic mechanism of ECT has been extensively studied, though continues to be elusive. As a result of ECT research in humans and electroconvulsive shock (ECS) in rats, evidence has accumulated showing that ECT significantly affects the HPT axis. A rapid increase in hypothalamic–pituitary activity occurs following ECT. Along with this activity, there is an associated increase in TSH secretion that correlates with duration of the ECT-induced seizure (Dykes et al., 1987; Scott et al., 1989; Whalley et
ECT. Measures of verbal learning and memory, remote depressant medications were discontinued for 7 d prior to either T3 or placebo during the course of ECT. Anti-disorder (depressed) who were randomized to receive euthyroid males with diagnoses of major depression, effects of ECT (Stern et al., 1991). Patients included 20 In a prospective study, our group then investigated the relationship between pre-ECT FTI levels and severity of post-ECT. Their results indicated a significant inverse correlation. Recently, Papakostas et al. (1999) found an inverse relationship between TSH response to TRH and seizure duration. That is, patients who had blunted TSH response to exogenous TRH had longer ECT seizures than those without blunted TSH responses.

**Combined thyroid hormone and ECT**

To further investigate the relationship between ECT and the HPT axis, Prange et al. (1990) retrospectively reviewed the charts of 50 psychiatric in-patients with normal free thyroxine indices (FTI) before undergoing ECT. Their results indicated a significant inverse correlation between pre-ECT FTI levels and severity of post-ECT confusion and memory disturbance, suggesting that relatively lower T4 levels prior to ECT were associated with significantly worse cognitive side-effects from ECT. In a prospective study, our group then investigated the effect of exogenous T3 on diminishing the cognitive side-effects of ECT (Stern et al., 1991). Patients included 20 euthyroid males with diagnoses of major depression, schizoaffective disorder (depressive type), or bipolar disorder (depressed) who were randomized to receive either T3 or placebo during the course of ECT. Antidepressant medications were discontinued for 7 d prior to ECT. Measures of verbal learning and memory, remote personal memory, and psychiatric functioning were administered at pretreatment (1–3 d pre-ECT) and post-treatment (7–10 d following the final treatment). Serum assays were performed for T3, T4, T3 uptake, and TSH at pretest and immediately before the final ECT. Patients were randomized in a double-blind manner and stratified for age, IQ estimate, and TSH level to receive either 50 μg liothyronine (synthetic T3) or placebo, beginning the night prior to the first ECT and continuing daily until the day of post-testing. There were 11 subjects in the T3 group and 9 in the placebo group. No significant differences between the groups were found for age, education, or pre-ECT depression severity ratings. All patients underwent a standardized ECT treatment protocol, with the treating psychiatrist blind to drug condition.

As expected, the T3 group had significantly increased T3 and decreased T4, FTI, and TSH on final ECT serum thyroid measures compared to pretreatment. No difference in thyroid functioning was seen in the placebo group over the course of ECT. Post-test neuro-psychological testing revealed that the T3 group learned more words and recalled more after a delay on the verbal learning task than the placebo group, but these differences failed to reach statistical significance. Significant differences were seen between T3 and placebo groups on the measure of remote personal memory, with the T3 group recalled more personal events than the placebo group. In addition to these cognitive effects, the T3 group required significantly fewer ECT treatments to obtain an antidepressant effect compared to the placebo group (mean = 8.0 vs. 12.2, respectively). Furthermore, there were no non-responders in the T3 group compared to 2 placebo patients who showed no clinical improvement after 12 treatments. Significant negative correlations were found between percent improvement of depression severity ratings and T4 level and FTI in the T3 group, indicating that the lower the T4 at post-test, the greater amount of improvement in depressive symptoms. Results from the Stern et al. (1991) study suggest that a 50 μg dose of T3 during the course of ECT diminishes the amnestic side-effects of ECT and appears to accelerate the antidepressant effects of the treatment.

Stern et al. (1991, 1993) offer two possible explanations for less severe memory impairment in the T3 group. First, the lack of memory deficit in the T3 group may merely reflect the fact that they received fewer ECT treatments. A direct relationship has been demonstrated between severity of cognitive impairment and the number of ECT treatments received (Daniel and Crovitz, 1983). However, it is also possible that changes in T4 availability in the brain serves as protection from amnestic side-effects. Decreases in central T4 have been shown to reduce...
neuronal actin polymerization, and replacement with exogenous thyroid hormone appears to normalize the process (Siegrist-Kaiser et al., 1990). Therefore, it is possible that temporary disorganization of neuronal actin cytoskeleton resulting from decreased T4 secondary to T3 administration protects synaptic connections from disruption caused by the seizure.

Stern et al. (1995) directly assessed whether decreased amnestic side-effects were related to fewer ECT treatments by examining the impact of combined administration of T3 and ECS on retrograde and anterograde memory in rats. Thirty-two Sprague–Dawley rats were divided into four groups: ECS/T3, sham-ECS/T3, ECS/placebo, and sham-ECS/placebo. Rats were given 1 mg of T3 or placebo administered intraperitoneally at a volume of 1 ml/kg body weight on the morning of each ECS or sham ECS. Rats in the ECS groups were administered shock via ear-clip electrodes after being lightly anaesthetized. Motor seizures lasted between 5 and 25 s. Control animals received sham ECS in which they were handled, had anaesthesia, and had ear clips applied. All animals underwent procedures on five occasions over a 10-d period.

An open-field apparatus (Hebb–Williams maze) was used to measure retrograde amnesia. Healthy rats initially placed in this apparatus will typically explore, but locomotor behaviour usually declines on subsequent exposures because of familiarity with the environment. If rats do not remember the apparatus, they will continue a high level of exploratory behaviour, which would indicate difficulty with retrograde amnesia. Pretreatment locomotor activity was measured and rats were assigned to conditions so that mean pretreatment locomotor activity levels were similar. The day after the last ECS or sham-ECS, locomotor activity was again measured. A passive avoidance (PA) apparatus was used to measure anterograde amnesia. Rats were initially trained to learn that if they stepped off a platform they would receive a foot shock. To determine whether animals learned, a test was conducted in which the same procedure was followed without delivery of a shock and latency to step down was recorded. Therefore, intact learning could be confirmed by longer step-down latencies.

Results of the Stern et al. (1995) study showed that all groups, except the ECS/placebo group, exhibited adequate retrograde memory functioning as evidenced by less exploration activity on the post-ECT open-field apparatus. Significantly less exploration was found for the ECS/T3 vs. ECS/placebo groups as well as sham-ECS/T3 vs. placebo groups. Results of the passive avoidance test showed that the ECS/T3 and sham-ECS/T3 groups had significantly longer step-down latencies compared with the ECS/placebo group. Only the ECS/placebo group exhibited anterograde amnesia. Results of this study suggest that administration of T3 appears to reduce ECS-related amnesia in rats, and that these effects are independent of the number of shocks administered because all animals received the same number of shock/sham exposure.

In a recent double-blind trial, Stern et al. (2000) attempted to replicate earlier findings that exogenous thyroid hormone could protect against ECT-related memory impairment. Thirty depressed patients (21 females, 9 males) undergoing ECT were randomly assigned to either 50 μg T3 (n = 14) or placebo (n = 16) daily throughout the course of ECT. Strict exclusion criteria were used. All patients underwent bilateral ECT using a standardized titration method. Memory functioning and depression severity were examined at points before, during, and after ECT course. At pre-treatment, groups did not differ in age and educational attainment, thyroid hormone levels, or severity of depression. There were no adverse effects reported by patients in the T3 group. Contrary to the preliminary study, no significant differences were found between the groups for antidepressant efficiency or efficacy, though because patients received fewer ECT treatments than in the previous study (in part due to changes imposed by managed care), there was limited variability, possibly reducing the ability to detect any significant changes. However, neuropsychological examination 1 d after the last ECT treatment revealed that patients taking T3 had significantly better verbal learning performance and remote memory than patients taking placebo. These findings confirm the results of the preliminary study, demonstrating that exogenous thyroid hormone appears to have neuroprotective effects during ECT.

Results from both animal and clinical studies using adjunctive thyroid hormone to protect against the amnestic effects of ECT are quite promising. Continued work into the potential mechanisms of thyroid hormone action in the CNS appears warranted. Further elaboration of the actin cytoskeleton hypothesis, seizure threshold effects, and potential effects on cerebral metabolism may help to identify the mechanism. Our group has focused on the use of exogenous T3 to protect against amnestic side-effects of ECT. However, given the recent findings that T4 and T3 used in combination improve cognitive and emotional functioning of hypothyroid patients beyond that of T4 alone, it may be worthwhile to examine this combination treatment for use with patients receiving ECT. Furthermore, given the anti-amnestic effects seen in our group’s studies, the potential use of thyroid hormone in amnestic disorders (e.g. Alzheimer’s disease) may also be an interesting area of research, one that our group has recently initiated. The combined use of T3 and ECT may
have significant clinical implications for the future of ECT, as well as possibly lead to insights into the mechanism of action of ECT and to a better understanding of the associated side-effects.

Conclusions

Lithium and ECT are highly effective treatments for patients with mood disorders. However, the use of these therapies is limited by their cognitive side-effects. Research evidence has accumulated demonstrating that the adjunctive use of thyroid hormone can potentially reduce these side-effects. It is anticipated that reducing cognitive side-effects of lithium and ECT will increase the availability of these therapies as well as improve patient satisfaction and compliance. There is also a potential to reduce utilization of expensive health-care resources by improving patient satisfaction with these psychiatric treatments.

References

treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology 137, 2490–2502.


Hahng CG, Pawlyk AC, Whybrow PC, Tejani-Butt SM (1999). Differential expression of thyroid hormone receptor isoforms by thyroid hormone and lithium in rat GH3 and B103 cells. Biological Psychiatry 45, 1004–1012.


ECT in schizophrenia and depression. *Psychiatry Research* 37, 5–10.


