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Brief report

Long term augmentation with T_3 in refractory major depression

Tammas F. Kelly [a,*], Daniel Z. Lieberman [b,c]

[a] The Depression and Bipolar Clinic of Colorado, 315 West Oak Street, Fort Collins, Colorado 80521, United States
[b] Department of Psychiatry and Behavioral Sciences, George Washington University School of Medicine and Health Sciences, United States
[c] Clinical Psychiatric Research Center, George Washington University, School of Medicine, 2150 Pennsylvania Avenue, NW Washington, DC 20037, United States

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Abstract

Background: The addition of triiodothyronine (T_3) is one of the most widely studied augmentation strategies for refractory depression. Despite this there are no long term studies or studies of doses above 100 mcg.
Method: Long term and high dose augmentation with T_3 for refractory unipolar major depression was studied. Seventeen patients were assessed for symptom improvement with the Clinical Global Impression of Improvement Scale.
Results: Fourteen of 17 patients showed improvement. One patient saw no improvement and 2 dropped out due to side effects. The patients who benefited showed an average CGI improvement of 2.5 (SD: 0.52). The average dose used was 80 mcg (SD: 30.2, range: 25 mcg–150 mcg). The average length of time on T_3 was 24.2 months (SD: 19.4, range: 11.8–86.7). This case series shows that T_3 may be successfully employed as a long term treatment augmentation of major depression if over time dosage levels are increased beyond the traditional 50 mcg.

Keywords: Major depression; Refractory depression; Augmentation; Thyroid; L-thyroxine; T_3

One of the most widely studied medications used for augmentation of antidepressant treatment is triiodothyronine (T_3) (Nierenberg et al., 2006) yet long term studies and studies of doses beyond 50 mcg are rare. Until this year the highest published dose of T_3 studied has been 62.5 mcg (Wilson et al., 1974) with the rest of studies limited to 50 mcg (Joffe and Sokolov, 2000). For example in the STAR∗D study the maximum dose was 50 mcg with a remission rate of 24.7% over an average of 9.6 weeks (Nierenberg et al., 2006). While the dose of T_3 has been limited, the dose of T_4 has been reported as high as 600 mcg and is recommended for routine use up to dose of 450 mcg (Bauer et al., 2003). Studies of high dose T_4 indicate the safety and tolerability of superphysiologic doses of thyroid hormone (Bauer et al., 2003).

Prior to this paper, Łojko and Rybakowski (2007) have studied the highest known dose of T_3 at 100 mcg for augmentation of antidepressants in 17 females with refractory depression. The full 100 mcg a day was added without titration, and included both bipolar and unipolar depression. Remission, defined as a Hamilton Depression Rating Scale (HDRS-17) ≤ 7, was achieved in 64.6% of patients. Partial response, defined as 50% reduction in HDRS-17 was seen in an additional 29% of patients. Only one patient failed to show improvement.

* Corresponding author. George Washington University, 315 West Oak Street, 5th Floor, Fort Collins, Colorado 80521, United States. Tel.: +1 970 484 5625; fax: +1 970 493 5131.
E-mail address: TamKellyNews@gmail.com (T.F. Kelly).

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1. Methods

In a clinic specializing in the treatment of refractory affective disorders all patients suffering from refractory highly recurrent major depression moderate or severe were offered augmentation with T_3. None of the patients suffered psychotic features.

The Poudre Valley Health System provided institutional review board approval. All patients had normal TSH levels. Refractory depression is defined in this paper as the failure to respond to greater than three adequate trials of antidepressants for the presenting episode of depression. Highly recurrent depression in this study is defined as greater than three life time major depressive episodes. Dosing started at 25 mcg and was adjusted every 2 to 3 weeks in 12.5 to 25 mcg increments as clinically indicated until remission was achieved. If response was lost this process was repeated with dosage increases of 12.5 mcg until response was maximized. Minimal tremor or minimal heat intolerance were the only acceptable hyperthyroid symptoms, otherwise, if symptoms of hyperthyroidism appeared the dose was reduced.

Data was collected in the author's private practice of routine clinical psychiatry. The data was abstracted from the patient charts without identifying information.

The diagnosis of Major Depressive Disorder was based on the DSM-IV criteria and clinical data was confirmed by family interviews and long term observation. The average length of time at the clinic was 6.5 years (SD: 3.8, range 1.7–12.3).

Treatment response was recorded using the Clinical Global Impression of Improvement scale (CGI-I): −3=very much worse, −2=much worse, −1=slightly worse, 0=unchanged, +1=slightly improved, +2=much improved, +3=very much improved. GAF scores were recorded at each appointment per clinic routine. The final GAF score reported was the last GAF score recorded before a cutoff date set arbitrarily for the preparation of the paper. Other medications were changed as clinically indicated.

2. Results

Seventeen patients accepted a trial of T_3, 10 females and 7 males, average age 48.7 (SD: 7.9, range: 37–62) (Table 1). The average length of time on T_3 was 24.2 months (SD: 19.4, range: 11.8–86.7). Two patients (11.7%) stopped treatment with T_3 due to side effects, one because of leg tremor and the other because of sluggishness, irritability and an increase of anxiety. One patient (5.8%) showed no improvement up to a dose of 125 mcg where further dosage increases were precluded by side effects. All of the patients who stopped T_3 augmentation because of side effects or failure to respond were male (43% of males). No females had to stop because of failure to respond or side effects. Fourteen patients benefited from T_3 with an average CGI-I score of 2.5 (SD: 0.52) (Table 2). The final average GAF score of all individuals who showed improvement was 76.2 (SD: 8.5, range: 62–90). Response was almost immediate when a threshold dose of either 25 mcg $n=7$ (50%), 37.7 mcg $n=1$ (7.1%), 50 mcg $n=3$ (21.3%), 62.5 mcg $n=2$ (14.2%) or in some cases 75 mcg $n=1$ (7.1%), was reached. The average dose of initial response was 42.0 mcg (SD: 17.8). Ten patients exceeded 50 mcg. The average dose was 80 mcg (SD: 30.2, range: 25–150).

Table 1
All subjects.

	All ($n=17$)	Male ($n=7$)	Female ($n=10$)	P (male vs. female)
Age	48.7 (7.9)	51.9 (9.1)	46.5 (6.5)	ns
Past medication count	14.8 (9.9)	13.4 (4.9)	15.7 (12.4)	ns

Refractory depression was defined in this paper as the failure to respond to greater than three adequate trials of antidepressants for the treatment of the presenting episode of depression. However, in actuality the number of failed medication trials experienced by patients in this study was far greater prior to the addition of T_3. The average number of medications tried before the patient entered the care of the clinic was 6.7 (SD: 5.16, range: 0–20). The average number of medication trials under the clinic's care was 8.1 (SD: 6.67, range: 1–26) (Table 2). These figures include both treatment failures and trials stopped because of side effects. One patient with marked improvement to T_3, CGI-I: +2, had previously received 2 ECT trials.

No patients developed ostopenia, osteoporosis or atrial fibrillation or any other major adverse events.

Adequate response was defined as a CGI-I ≥ 2 lasting 2 or more months. Response was lost 24 times in 10 patients. The average length of time prior to loss of response was 5.8 months (SD: 6.7, range: 2–26). There were no statistically significant differences between genders. Following loss of response, T_3 was increased in 12.5 mcg increments until previous response or better was reached. In each case the initial improvement was recovered or exceeded. In 10 patients (58%) who showed response, T_3 was the last medication added and in one other patient (5.8%) T_3 was the last medication

Table 2
Clinical variables: comparison of male and female subjects responding to T_3.

	All (n=14)	Male (n=4)	Female (n=10)	P (male vs. female)
Age	48.7 (7.7)	52.5 (9.8)	47.2 (6.7)	ns
Past medications	14.8 (9.9)	13.4 (4.9)	15.7 (12.4)	ns
T_3 dose	79.0 (36.0)	78.1 (38.7)	79.4 (37.0)	ns
Length in months	24.2 (19.4)	14.8 (1.9)	28.0 (22.0)	ns
CGI-I	2.5 (0.52)	2.5 (0.58)	2.5 (0.53)	ns
Initial GAF	61.0 (8.0)	66.2 (6.6)	58.9 (7.8)	ns
End GAF	76.2 (8.4)	80.8 (9.7)	74.4 (7.7)	ns
GAF change	15.2 (7.6)	14.5 (4.5)	15.5 (8.8)	ns
Remission	35.7%	50%	30%	ns

increased. Other medications were used in the patients in this study in addition to T_3. These included 12 patients who received lamotrigine, five who received buspirone, oxcarbazepine, or venlafaxine extended release, four who received lorazepam or zolpidem, three who received amphetamine/dextroamphetamine or mixed salts aripiprazole, two who received carbamazepine, escitalopram, modafinil, sertraline, tranylcypromine or trazodone and one each who received amitriptyline, bupropion sustained release, citalopram, clonazepam, fluoxetine, gabapentin, mirtazapine, paroxetine, pramipexole, or triazolam.

3. Discussion

This observational study while limited in size and scope had the advantage of a stable population followed over a long period of time. Other medications were changed as needed. While long term and high dose studies of T_4 exist (Bauer et al., 2003), this is the first report in which T_3 was used in doses up to 150 mcg, and the first to report long term benefit. The results suggest the clinical utility of a full range of T_3 augmentation including high dose T_3 in highly recurrent refractory depression. Furthermore, the results suggest that the benefit can be sustained long term. This study corroborates the strong results seen in Łojko and Rybakowski's (2007) study that used a fixed dose of 100 mcg but was limited to 4 weeks.

While time alone, or treatment with concurrent medications, may account for the improvements seen there are multiple reasons to conclude that treatment with T_3 was primarily responsible. The dramatic improvement at the time of T_3 initiation or following dosage increases is most compelling. In addition, the prior history of a large number of failed trials of medications, and the loss of efficacy and subsequent reappearance of response following an increase of the T_3 dose argues for the efficacy of this approach.

Of note 43% of males, 3 of 7, discontinued T_3, two because of side effects and one with failure to respond. All females responded. This supports the findings from Altshuler et al.'s, (2001) meta-analysis that women are more likely than men to benefit from the addition of T_3.

In the majority of patients 10/14 (71%), the initial positive response was subsequently lost. This may represent the down regulation of the thyroid gland's output of endogenous thyroid as the result of the external application of T_3. In each of these 10 patients upward readjustment of the T_3 dose re-established full and sustained benefits. The final dose exceeded 50 mcg in 10 patients, supporting the utility of higher doses. The benefit of long term augmentation is shown.

The thyroid axis is dynamic and self regulating. In the face of exogenous applied thyroid the thyroid gland may decrease output of endogenous hormone. This suggests that higher doses of T_3 may be needed over time to maintain benefit and fits with the results of the paper.

Finally, Wilson et al. (1974) found T_3 augmentation at 50 mcg was associated with significant improvement, but when the T_3 dosages were raised to 62.5 mcg their study group actually worsened. These authors hypothesized the deterioration was due to thyroid toxicity. However this conclusion runs counter to both Łojko and Rybakowski (2007) and this paper's findings that T_3 augmentation, even at high dose (ave 80 mcg and max 150 mcg), was well tolerated with only 2/17, 12% patients stopping because of side effects.

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Conflict of interest

Neither authors have any ties to manufacturer of triiodothyronine. Tammas F. Kelly has received honoraria from GlaxoSmithKline and AstraZeneca. Daniel Z. Lieberman has received grant support from AstraZeneca, Comentis, Eli Lilly, Epix, McNeil, Ono, Predix, Sanofi Aventis, Wyeth, and The Dalio Family Foundation, and has received honoraria from GlaxoSmithKline.

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