Depression and thyroid hormones :

new findings need a new understanding

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On the road of solving the puzzle



diagnosis of depression

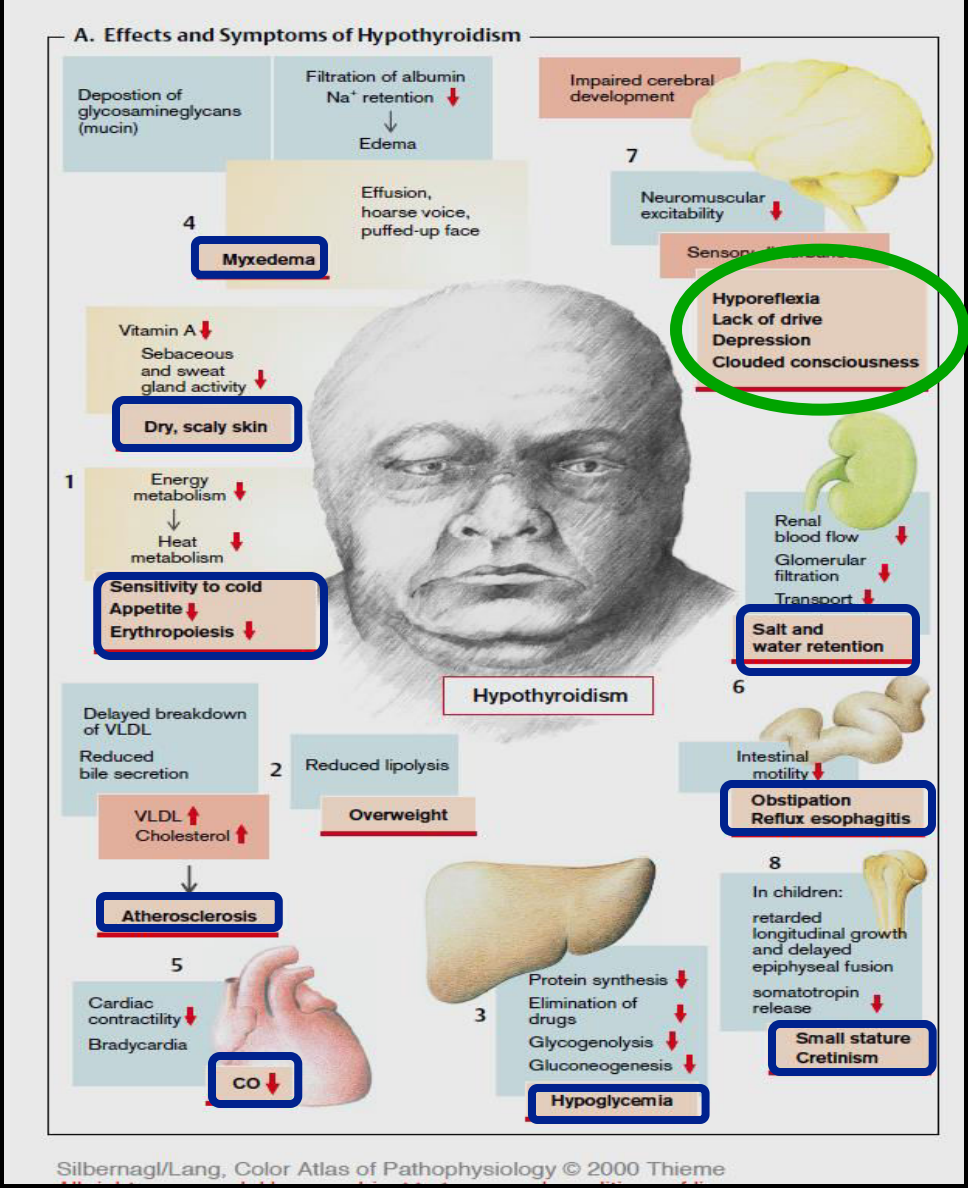
At least *5* *depressive* *symptoms* , for at least *2 weeks* .

clinically significant distress or impairment in *social, occupational,* or other important *areas of functioning.*

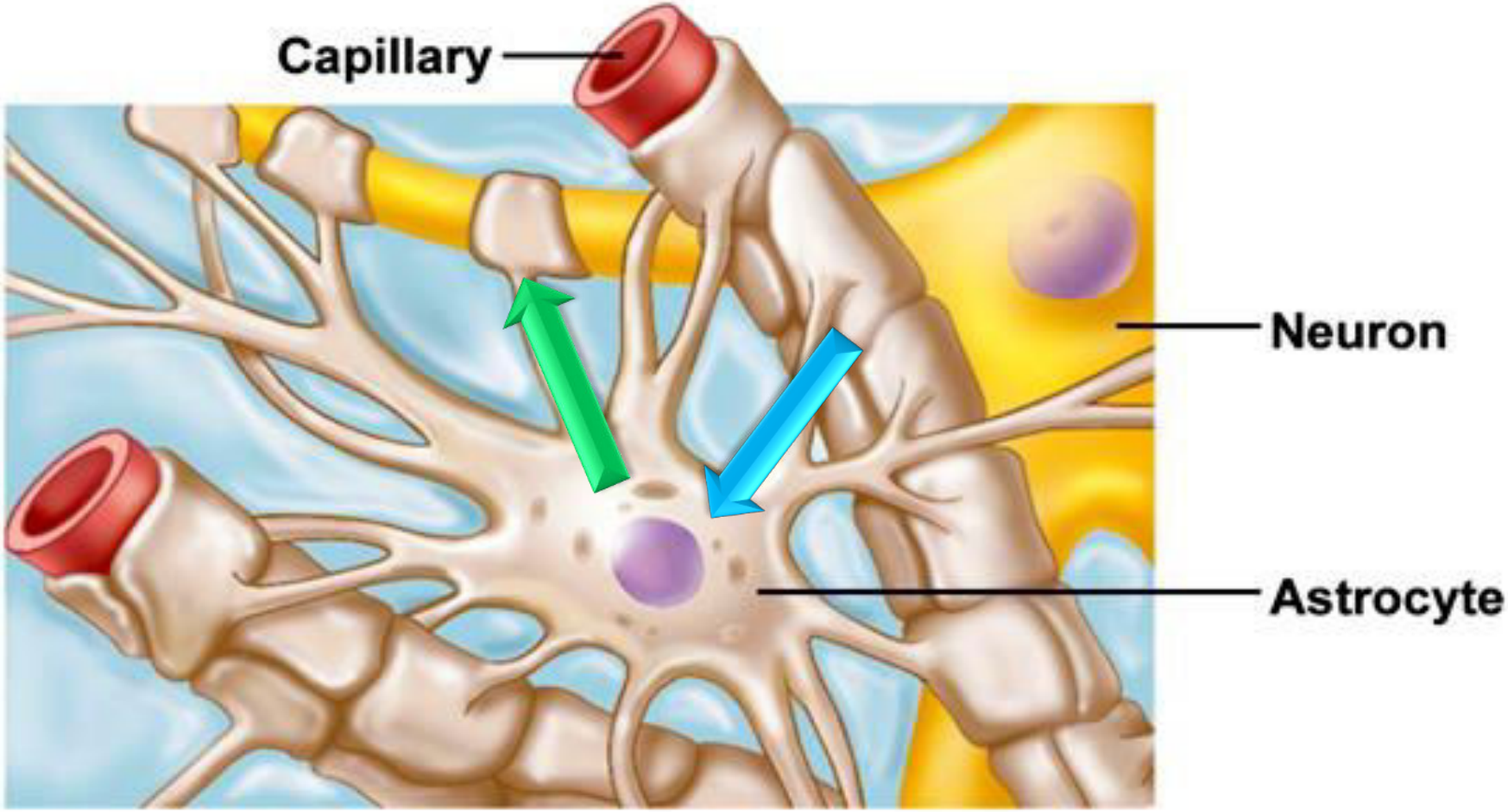
The episode is not attributable to the physiological effects of a *substance* or another *medical condition.*

Brain hypothyroidism

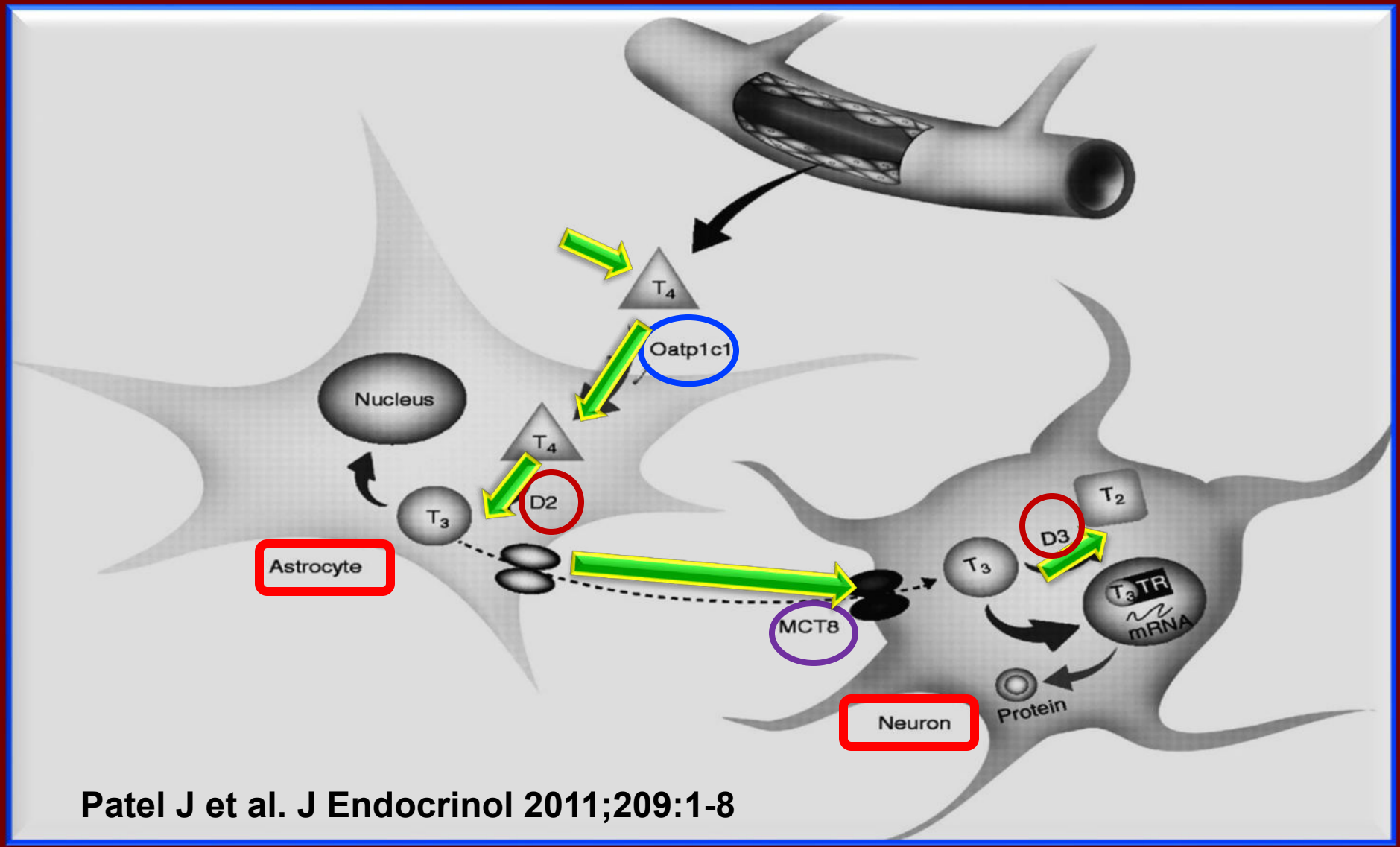
Neuropsychiatric Manifestations of Hypothyroidism



Blood Brain Barrier



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Patel J et al. J Endocrinol 2011;209:1-8

(Oatp 1c1) : Organic Anion Transporting Polypeptide type 1c1

(D2) : De-iodonase type 2 (MCT8) : mono-carboxylase transporter 8

Neuropsychiatric Manifestations of tri-iodothyronine (T3)

- In ***patients of hypothyroidism treated with T4*** , ***psychological symptoms*** may ***persist*** even when they achieve the **euthyroid state** [1].

- According to the **American Association of Clinical Endocrinologists**, "**The diagnosis of subclinical or clinical hypothyroidism must be considered in every patient with depression**" [2].

[1] . P. Saravanan, W. F. Chau, N. Roberts, K. Vedhara, R. Greenwood, and C. M. Dayan, "Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study," Clinical Endocrinology, vol. 57, no. 5, pp. 577–585, 2002.

[2]. H. J. Baskin, R. H. Cobin, and D. S. Duick, "American association of clinical endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism," Endocrine Practice, vol. 8, no. 6, pp. 457–469, 2002.

how could "brain hypothyroidism "be detected ?

- ***lower levels*** of ***CSF trans-thyretin (TTR)*** have been reported in patients with ***depression*** compared to controls resulting in a state of ***" brain hypothyroidism"*** with, normal peripheral thyroid hormones [1].

- ***Mutations*** in ***mono-carboxylase transporter 8*** **(MCT8)** have also been recognized to cause isolated ***brain hypothyroidism*** by blocking T3 transport into neurons [2]

[1] J. A. Hatterer, J. Herbert, C. Hidaka, S. P. Roose, and J. M. Gorman, "CSF transthyretin in patients with depression," *American Journal of Psychiatry*, vol. 150, no. 5, pp. 813–815, 1993.

[2,]. T. Suzuki and T. Abe, "Thyroid hormone transporters in the brain," *Cerebellum*, vol. 7, no. 1, pp. 75–83, 2008.

how could "brain hypothyroidism "be detected ?

- ***Type 2 deiodinase disruption in astrocytes results in anxiety-depressive-like behavior in male mice.***

- Both **tricyclic antidepressants [2]** and **SSRIs [3]** appear to **enhance the activity of D2** resulting in an increased ***conversion of T4 into active T3 in the brain***.

[1] Bocco BM, Pedro Werneck-de-Castro J, Oliveira KC, Fernandes GW, Fonseca TL, Nascimento BP, McAninch EA, Ricci E, Kvárta-Papp Z,Fekete C, Martha Bernardi M, Gereben B, Bianco AC, Ribeiro MO. *Endocrinology. August 8, 2016. PMID: 2750118.*

[2] . A. Campos-Barros, H. Meinhold, M. Stula et al., "The influence of desipramine on thyroid hormone metabolism in rat brain," *Journal of Pharmacology and Experime*Baumgartner, M. Dubeyoko, A. Campos-Barros, M. Eravci, and H. Meinhold, "Subchronic administration of fluoxetine to rats affects *ntal Therapeutics*, vol. 268, no. 3, pp. 1143–1152, 1994.

[3,]. A. triiodothyronine production and deiodination in regions of the cortex and in the limbic forebrain," *Brain Research*, vol. 635, no. 1-2, pp. 68–74, 1994.

Role of antidepressants in treatmen of (Brain Hypothyroidism)

- T3 was suggested to enhance neurotransmission in the central ***noradrenergic pathways*** [1] and deficiency in catecholamines has been raised as a possible mechanism in depression [2].

[1] . P. C. Whybrow and A. J. Prange Jr., "A hypothesis of thyroid-catecholamine-receptor interaction. Its relevance to affective illness," Archives of General Psychiatry, vol. 38, no. 1, pp. 106–113, 1981.
[2] . C. A. Kicey, "Catecholamines and depression: a physiological theory of depression," *American Journal of Nursing*, vol. 74, no. 11, pp. 2018–2020, 1974.

Uses of T3 (Liothyronine) in depression

- ***In the initial few weeks of an antidepressant trial*** to reduce the delay in antidepressant effect - ***acceleration studies***

- ***To improve treatment response*** in those who do not respond adequately to an antidepressant trial - ***augmentation studies***

- ***To enhance antidepressant response*** by being used throughout the antidepressant trial - ***enhancement studies.***

Study	N	T3 dose (μg/day)	Design	Result
Appelhof et al, 2004[45]	113	25 vs 50	RCT, placebo-controlled	T3 25 μg=T3 50 μg=Placebo
Cooper Kazaz et al, 2007[46]	124	50	RCT, placebo-controlled	Response T3=70%, Placebo=50%
Posternak et al, 2007[47]	50	50	RCT, placebo-controlled	Response T3=51%, Placebo=33%

Sequenced Treatment Alternatives to Relieve Depression - (STAR*D) Study

Level 1 : Citalopram 33 % remission

Level 2 :

Switch : Bupropion-SR / Sertraline / Venlafaxine-XR / CBT 25 % remission

Augment : Bupropion-SR / Buspirone / CBT 30 % remission

Level 3 : Switch : Mirtazepine / Nortriptyline

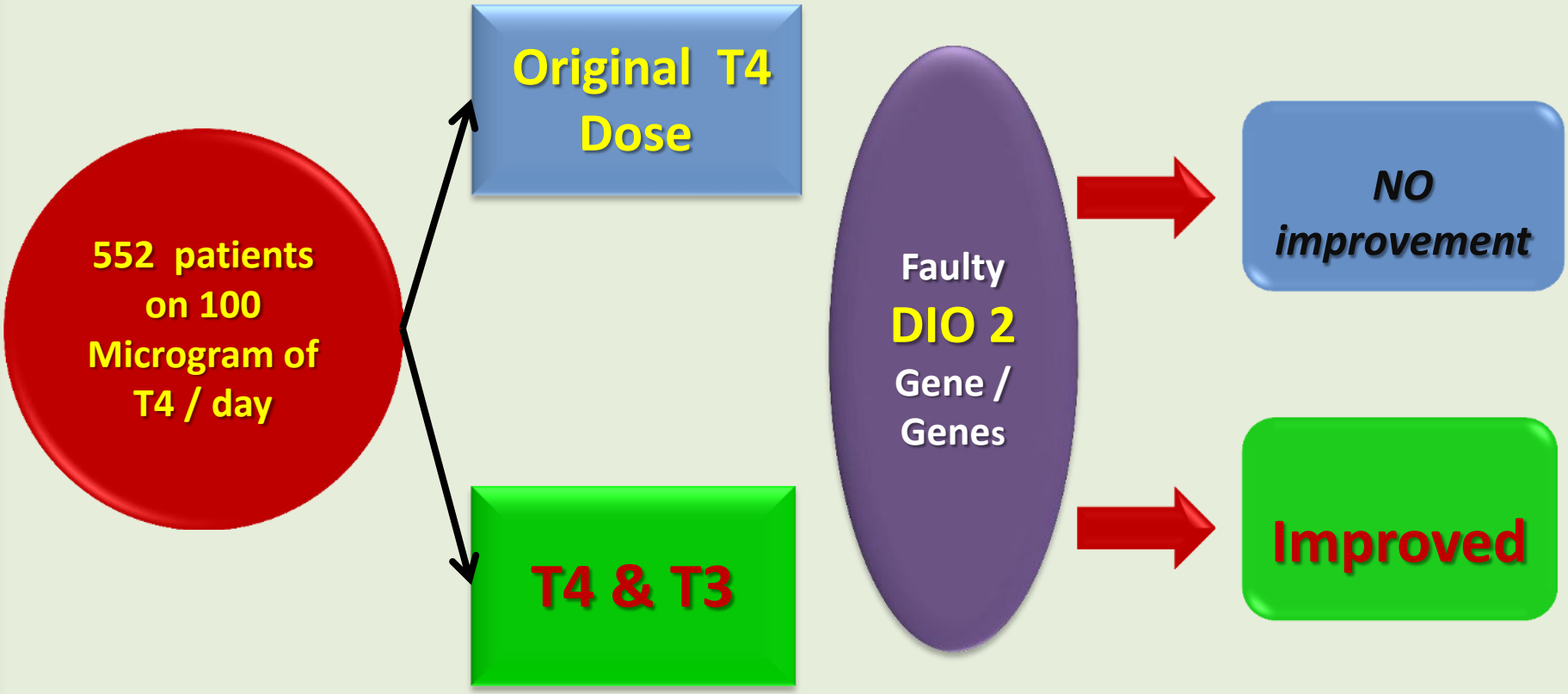
Augment : lithium 16 % remission / T3 25 % remission

Level 4 :

Switch : Venlafaxine + Mairtazepine 14 % remission

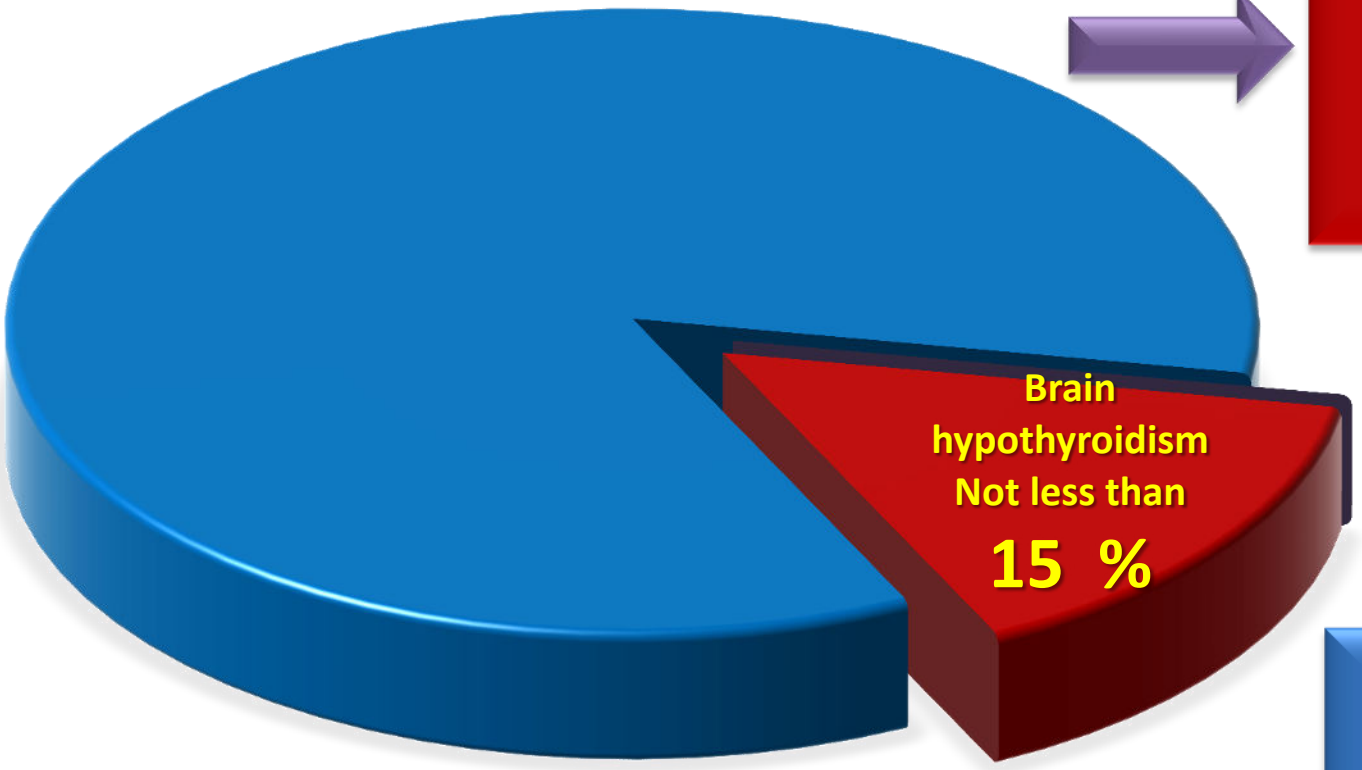
Or Tranylecypromine 7 % remission

ROLE of T3 in brain hypothyroidism



V Panicker, P Saravanan, B Vaidya, J Evans, A Hattersley, T Frayling & C Dayan,"Common Variation in the DIO2 Gene Predicts Baseline Psychological WellBeing and Response to Combination Thyroxine Plus Triiodothyronine Therapy in Hypothyroid Patients " J Clin Endocrinol Metab, May 2009, 94(5):1623–1629.

Brain hypothyroidism in psychiatry : the current vs the ideal



Resistant Depression

Mood disorder due to another medical condition

Saint-Clair Bahls a and Gisah Amaral de Carvalho,"The relation between thyroid function and depression: a review" Rev Bras Psiquiatr 2004 ; 26 (1) : 40-8

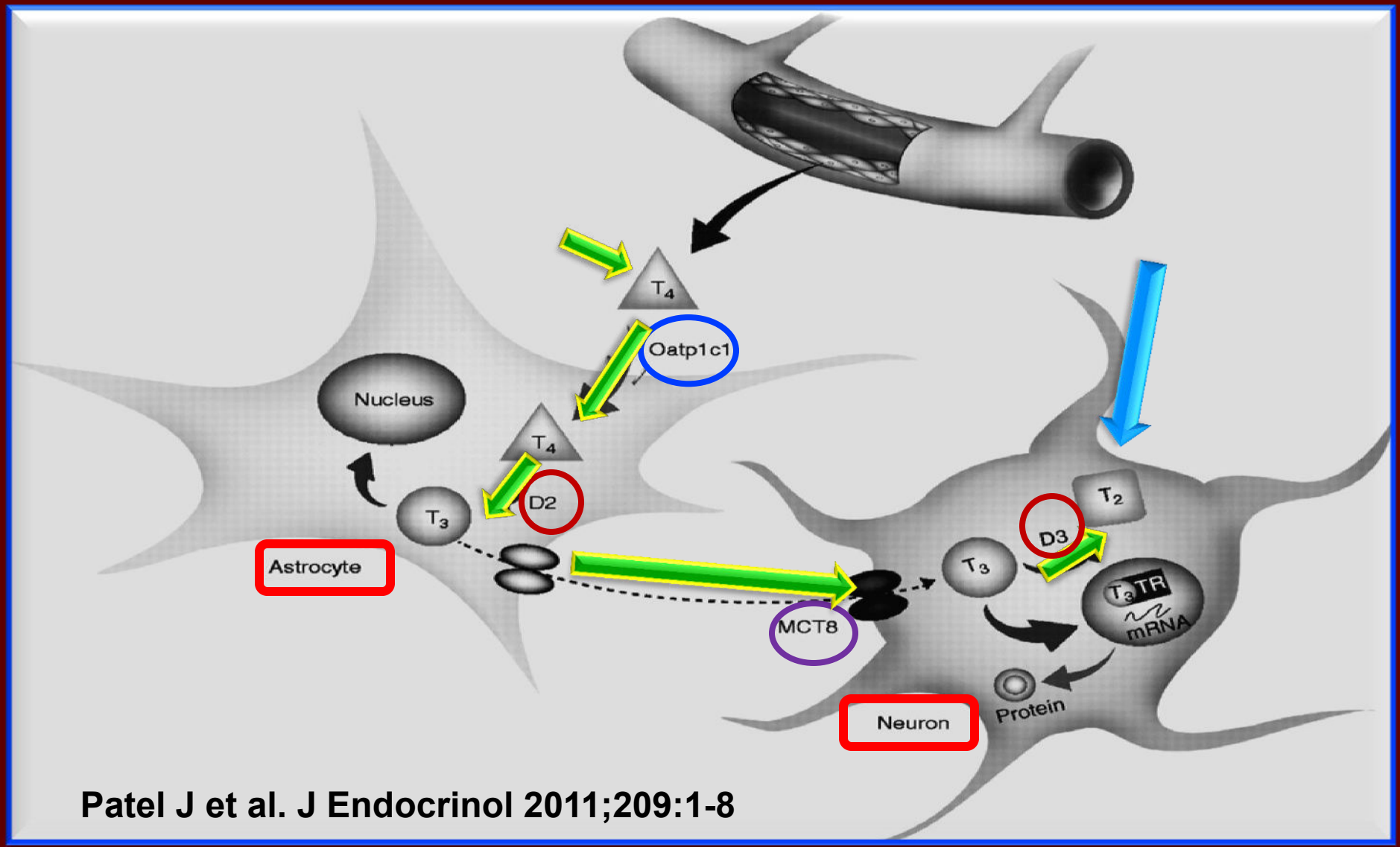
Is there a place for symptomatology in finding out patients with "Brain Hypothyroidism"





Atypical depression

Seasonal Affective Disorder

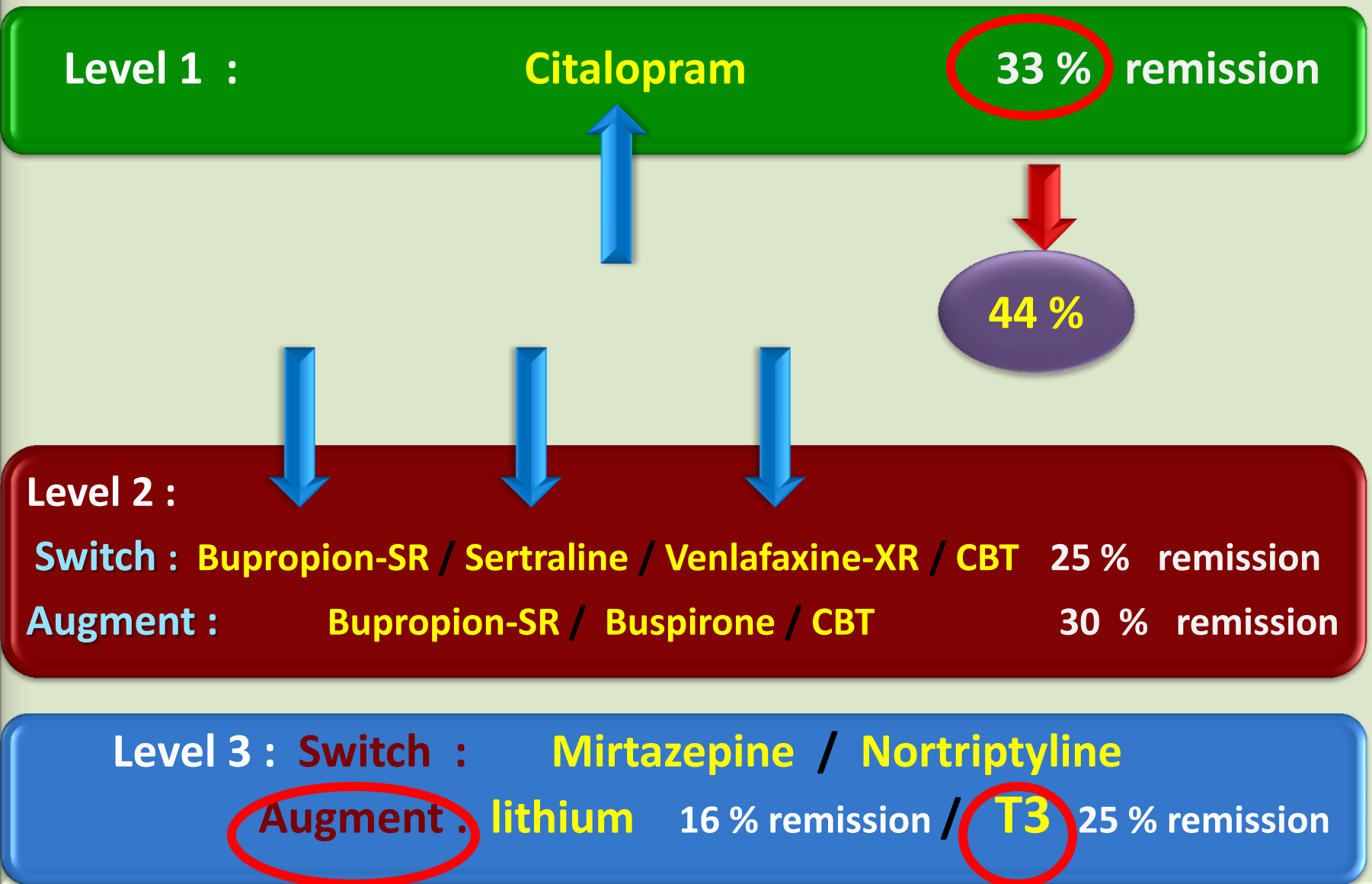


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Sequenced Treatment Alternatives to Relieve Depression - (STAR*D) Study



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Conclusion

- **" Brain hypothyroidism " may explain why some cases of depression are resistant to treatment with the antidepressants .**

- **The suffering** of the patients with **" Brain hypothyroidism " will persist** till finding an easy way to **diagnose them early** and hence giving them the ***monotherapy*** **they need (i.e T3) .**

- **Psychiatric disorders (and manifestations) are more biological in their origin than what is considered .**

- **Being aware about the *nature of problem* we are facing , is the first step to solve it .**

Thank you

