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MULTIPLE ENDOCRINE RESPONSES TO CLONIDINE IN OBSESSIVE COMPULSIVE DISSORDER

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Seventy two subjects with OCD were compared with 18 normal healthy volunteers on multiple neuroendocrine responses to clonidine. Significant heterogeneity in OCD was observed in responses of growth hormone. There was also significant disturbances in cortisol and ACTH release. An interactional model for noradrenergic and serotonergic dysfunction in OCD is discussed.

Obsessive Compulsive Disorder (OCD), although initially tought to be a relatively uncommon disease, is now recognised to occur in about 3% of the general population (Myers *et al.*, 1984). It is not surprising therefore that there is increasing interest in the biological basis of this disorder (Zohar *et al.*, 1987, 1988). Most of this interest has focused on the neurochemistry of the disorder. The most convincing evidence which currently exists implicates the serotonergic system in the form of [1] abnormalities of ^{3}H-imipramine binding, [2] reduction CSF 5-hydroxy indole acetic acid levels, [3] exacerbation of symptoms with a serotonergic agonist - m-chlorophenylpiperazine, with a blunting of neuroendocrine responses; a change which normalises after treatment with clomipramine/ fluvoxamine and [4] response to serotonin uptake inhibitors and precursors (Khanna, 1988; 1992 and Zohar and Insel, 1987). However it is widely accepted that the serotonergic model does not explain all abnormalities in OCD as treatment non-responders are recognised. The most extreme position is probably adopted by Marks (1987) who believes that the effect of serotonin uptake inhibitors is only in the associated depression and has no effect on the obsessive compulsive state per se.

There is, in addition, some evidence to suggest that there may be a noradrenergic dysfunction in OCD, as in depression. A blunted growth hormone response to clonidine in OCD has been reported (Siever *et al.*, 1983). While Hollander *et al.* (1988) reported subjective improvement after intravenous administration of clonidine, they subsequently did not corroborate this with the hormonal correlate (Hollander, 1988). In addition there exist reports of the clinical efficacy of clonidine in single cases (Knesevich, 1982; Hollander *et al.*, 1988; Lipsedge and Prothero, 1987) and open trials (Rao and Rao, 1988; Khanna 1990). Clonodine is also found efffective in treatment of Gilles de la Tourette syndrome, a disorder thought to be allied in many respects with OCD (Khanna *et al.*, 1987). Lee *et al.* (1990) found an increased number of alpha-2 receptor binding sites to ^{3}H-clonidine in platelets in OCD. There thus exists a strong body of evidence to suggest that there may be noradrenergic dysfunction in OCD, which however has not been adequately explored so far.

One of the strategies commonly used in studying noradrenergic function in depression is the neuroendicrine response to clonidine (Siever and Uhde, 1984). The measure most commonly used in the growth hormone response. However it is now recognised that there is alpha-2 adrenergic involvement in the control of several other hormones, specifically cortisol, ACTH and perhaps prolactin (Bennett and Whitehead, 1983) and consistent changes in these parameters have been reported in nor-

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mals (Khanna *et al.*, 1990). There have been recent reports of the usage of such strategies as marker of the noradrenergic dysfunctional state in melancholic depression (Amsterdam *et al.*, 1989). The usage of multiple neuroendocrine marker in response to alpha-2 agonists like clonidine helps assessing both pre and post-synaptic noradrenergic functions.

The current study is an attempt at exploring noradrenergic function in OCD using multiple neuroendocrine responses to clonidine and determining whether there are different subgroups based on noradrenergic function in OCD.

METHODOLOGY

PATIENTS

The patients included in this study met DSM III criteria for OCD (American Psychiatric Association, 1980). Patients characteristics are given in Table 2. Subjects who had Hamilton Depression Scores (Hamilton, 1960) greater than 11 were excluded from the study. All subjects gave written consent to participate in this study. None of the patients had any major co-existent physical disorder such as hypertension. Patients with history suggestive of other co- morbid psychiatric disorders, such as Panic Disorder, or Alcohol abuse and dependence were also excluded from this study. Subjects were rated onLeyton's Obsessional Inventory (Copper, 1970) and the scores are given in Table 2. Subjects who had only obsessions and those with obsessions and compulsions were regarded as two separate groups. The duration of illness ranged from 0.6 to 14 years. All patients were drug free for a minimum period of 4 weeks prior to the conduct of this study. None of the patients had a past history of tic disorder or major depression which was not secondary to OCD or had psychotic or endogenous features. There were no clinically significant laboratory findings. All subjects were within 20% of their ideal weight. None of the subjects had a past clinical history of hepatic, renal, endocrinological or cardiovascular illness. None of the female subjects were on oral contraceptives, but the study was conducted irrespective of the period of their menstrual cycle. There were a total of 72 subjects with OCD who participated in this study.

HEALTHY VOLUNTEERS

Eighteen drug-free healthy controls formed the normal sample for this study. They were recruited from the employees of the institute. Sociodemographic details are given in Table 1. All of the subjects were studied under similar experimental conditions. None of the subject had any coexistent or past history of psychiatric illness. All were free of major physical illness at the time of conducting this investigation and none had a past history of endocrines, hepatic, renal or cardiovascular disorder. Further there was no historical evidence of psychiatric morbidity in their first degree relatives.

Table 1 : Sample charateristics

Population	N	Age	Male: Female	LOI Score
Normal	18	19-43 (25.4 S.D. 5.2)	11:7	
OCD-Total	72	17-51 (24.6 S.D. 7.8)	41:31	46-59 (53.1 S.D. 6.2)
OCD-Obsessions	21	17-42 (21.8 S.D. 5.2)	14:7	46-53 (54.1 S.D. 4.2)
OCD Compulsions	51	19-51 (23.8 S.D. 9.1)	24:24	47-59 (52.7 S.D. 7.3)

PROCEDURE

All tests were conducted between 9 and 10 a.m. after an overnight fast. Clonidine hydrochloride, in a dose of 2 microgram/Kg body weight was diluted in 10 cc of normal saline and slowly infused, through a heparin locked i.v. catheter. Clotted blood for hormone assay was collected at 0, 15, 30 and 60 minutes. Some subject experienced transient drowsiness during the study, but no other side effect was reported.

Details of hormone kit characteristics, with regard to intra and inter-assay coefficient of variation and the sensitivity are given in table 2. Growth hormone (GH) concentration were determined by means of a double antibody radio- immuno assay technique by kits obtained from Bhabha Atomic Research Centre, Bombay. Cortisol concentrations were determined by a single antibody radio-immunoassay technique using kits obtained from Leeco Diagnostics, Michigan, USA. Prolactin concentrations were determined by a double antibody radio-immunoassay technique with kits obtained from Leeco Diagnostics, Michigan, USA. ACTH concentrations were also determined by a double antibody radio-immuno assay technique using kits obtained from Diagnostics Products Corporation, Los Angeles, USA. All assays involving samples from the same subjects were simultaneously performed in duplicate.

Table 2 : Hormone kit characteristics

Hormone	Coefficient of variation		Sensitivity
	Intra-assay	Inter-assay	
GH	6.4	6.2	0.3 ng/ml
Cortisol	6.29	6.32	0.21micro G/dl
Prolactin	4.2	2.5	0.9 ng/ml
ACTH	2.7	2.2	14 pg/ml

All assays done by radio immuno assay

STATISTICAL PROCEDURES

Growth hormone, cortisol, ACTH and prolactin levels are compared [1] between normal and the whole OCD sample and [2] between pure obsessionals and compulsives. The parameters taken for initial analysis were [1] baseline values, [2] maximal value and [3] maximal change from baseline [Delta-Max]. The comparison was done using t test.

We also performed Analysis of Variance (ANOVA) between [1] normals and the total OCD sample and [2] pure obsessionals and compulsives. ANOVA was performed for group, time and group x time (two way ANOVA).

Correlation was also done for baseline and delta-max hormonal values and Leyton's Obsessional Inventry scores.

RESULTS

There was significant blunting of the growth hormone response to clonidine when the whole OCD group was considered (Table 3, Figure 1), but there was no statistically significant baseline difference. Subsequently subjects were divided into those whose growth hormone response was more than 10 ng/ml (Augmenters) and less than 5 ng/ml (Blunted response).The intermediate group was regarded as having response similar to controls (no response) as shown in Table 4. There was a significant excess of blunted response in pure obsessional and augmented response in compulsive subjects.

There was no significant differences in the prolactin response between normal and OCD subjects (Table 5, Fig. 2). The cortisol response was significantly less in all OCD

groups as compared to normals (Table 6, Fig. 3). The ACTH response was significantly lowerd for the pure obsessional group although this trend was observed for all OCD subjects (Table 7, Fig. 4). There was no significant correlation between scores in Leyton's Obsessional Inventory and baseline and delta-max hormone values.

On ANOVA, there was significant group differences betweeen OCD and normals for growth hormone, cortisol and ACTH. Time differences were significant only for growth hormone and ACTH. Two way ANOVA showed that there were significant differences for growth hormone, cortisol and ACTH (Table 8).

When pure obsessionals were compared with compulsives (Table 9) groups, time and interactional differences were observed mainly for ACTH.

Table 3 : Growth hormone responses to clonidine (ng/ml)

Group	Baseline	Peak	Delta-max
Normal	1.84 (1.16)	12.32 (4.18)	10.48 (5.41)
OCD-Total	2.11 (1.32)	9.31 (3.44)	7.20 (3.36)
OCD-Compulsions	2.18 (1.16)	9.44 (3.33)	7.26 (3.91)
OCD-Obsessions	2.09 (1.54)	9.11 (4.02)	7.02 (4.11)

Normal comparisons with other groups $p < 0.05$

Table 4 : Patterns of Growth hormone response to clonidine

OCD-group	Peak	Delta-Max	Obsessions: Compulsions
Augmenters	12.4	10.3	4:26
No Response	9.4	7.2	1:12
Blunted	5.9	3.9	16:14

Table 5 : Prolactin responses to Clonidine (ng/ml)

Group	Baseline	Peak	Delta-max
Controls	7.14 (4.22)	13.46 (6.31)	6.32 (5.28)
OCD-Total	6.62 (5.11)	12.11 (5.29)	5.49 (4.88)
OCD Obsessions	6.74 (4.96)	13.01 (6.32)	6.27 (4.93)
OCD Compulsions	6.57 (5.22)	11.74 (5.11)	5.17 (5.16)

All comparosons are non-significant

Table 6 : Cortisol response to clonidine (micro G/dl)

Group	Baseline	Peak	Delta-Max
Controls	13.14 (6.32)	7.32 (3.44)	5.82 (5.21)
OCD-Total	11.93 (7.14)	5.44 (4.92)	6.49 (4.78)
OCD Obsessions	12.11 (6.99)	5.31 (4.78)	6.80 (4.32)
OCD Compulsions	11.86 (7.24)	5.49 (4.74)	6.37 (4.44)

Table 7 : ACTH response to clonidine (pg/ml)

Group	Baseline	Peak	Delta-Max
Controls	24.32 (15.14)	17.44 (11.32)	6.88 (9.16)
OCD-total	25.15 (16.16)	16.69 (12.22)	8.46 (7.11)
OCD-Obsessions	25.68 (15.92)	15.87 (7.44)	9.81 (6.17)
OCD-Compulsions	24.93 (16.01)	17.02 (10.07)	7.90 (7.12)

Table 8 : ANOVA for endocrine measures (Normals versus OCD)

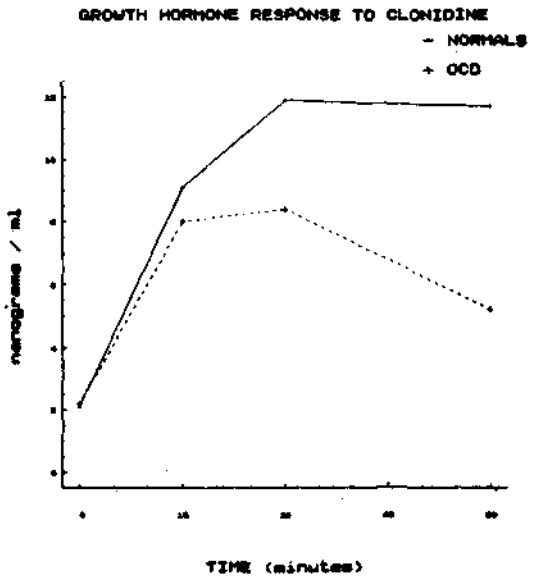
Term	F	d.f.	p
Growth hormone			
Group	21.9789	1,88	<0.0001
Time	11.3246	3,356	<0.0001
Group x Time	10.4944	3,356	<0.0001
Cortisol			
Group	9.06709	1,88	<0.0034
Time	2.24247	3,356	<0.0832
Group x Time	2.93758	3,356	<0.336
Prolactin			
Group	0.56755	1,88	<0.4531
Time	2.15566	3,356	<0.3968
Group x Time	0.51858	3,356	<0.6724
ACTH			
Group	6.07161	1,88	<0.0157
Time	3.22398	3,356	<0.0231
Group x Time	1.3186	3,356	<0.0001

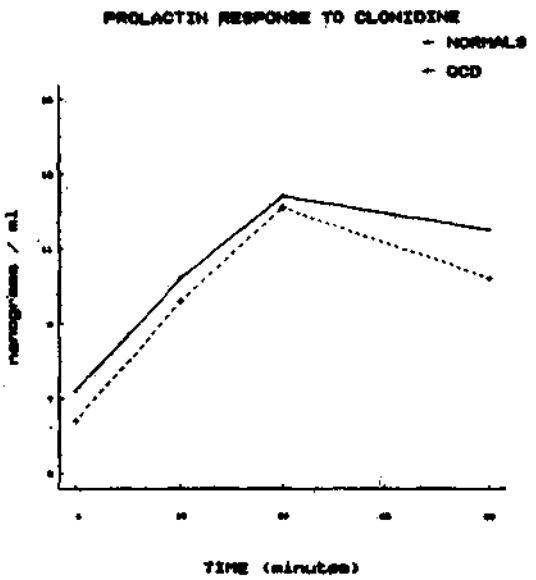
Table 9 : ANOVA for endocrine measures (Pure Obsessionals versus Compulsives)

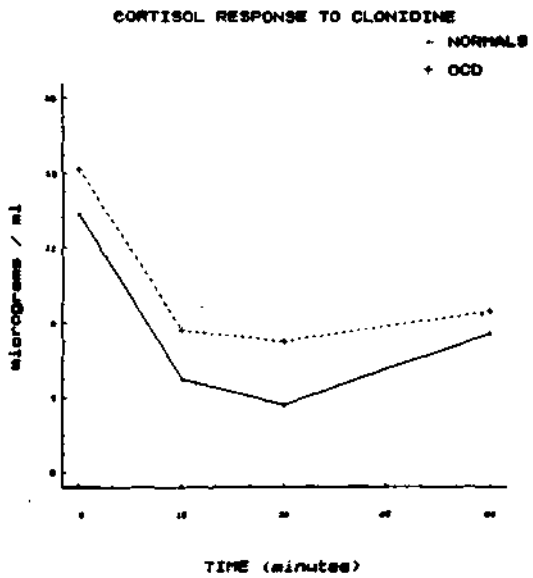
Term	F	d.f.	p
Growth hormone			
Group	3.19191	1,70	0.0784
Time	11.40388	3,212	<0.0001
Group x Time	2.18370	3,212	0.0911
Cortisol			
Group	3.99032	1,70	0.0497
Time	3.07043	3,212	0.0291
Group x Time	2.02101	3,212	0.1121
Prolactin			
Group	1.02761	1,70	0.3142
Time	2.44934	3,212	0.0648
Group x Time	0.723661	3,212	0.5441
ACTH			
Group	6.35536	1,70	0.0134
Time	9.73842	3,212	<0.0001
Group x Time	5.20598	3,212	0.0018

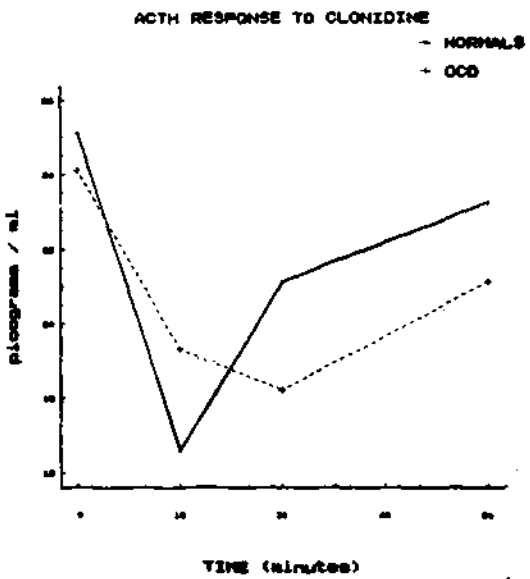
DISCUSSION

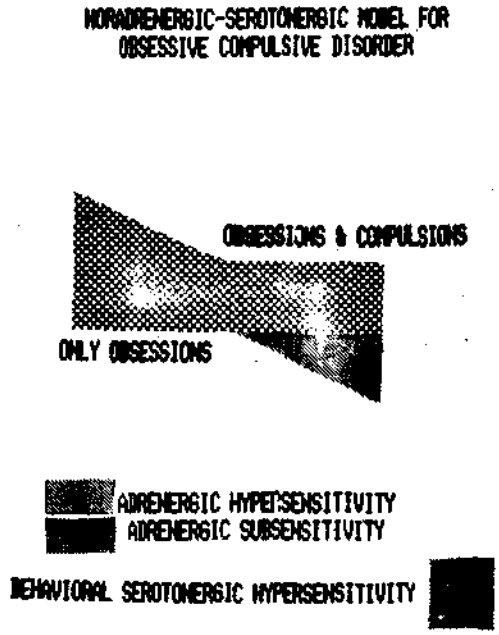
As has been discussed in the introduction, there is very strong evidence which implicates serotonergic dysfunction in OCD. Although it was initially thought that it is the $5HT_{1B}$ receptor which undergoes behavioural upregalation (Zohar *et al.*, 1987) this was later believed to be the $5HT_{1C}$ receptor since the former was not identified in the human brain (Kahn and Wetzler, 1991). There however continues to be controversy regarding the exact receptor mechanism of action of mCPP in the human brain (Kahn and Wetzler, 1991), and the maximum which can be stated that some 5 HT


GROWTH HORMONE RESPONSE TO CLONIDINE
- NORMALS
+ OCD
nanograms / ml
TIME (minutes)


PROLACTIN RESPONSE TO CLONIDINE
- NORMALS
+ OCD
nanograms / ml
TIME (minutes)


CORTISOL RESPONSE TO CLONIDINE
- NORMALS
+ OCD
micrograms / ml
TIME (minutes)





receptor subtypes are likely to be involved in the neurobiology of OCD (Murphy *et al.*, 1990).

Neverthless the current study documents noradrenergic dysfunction in OCD. When taken as a whole it appears that there is noradrenergic down-regulation in OCD, as initially reported (Siever *et al.*, 1983). Nevetheless when the OCD group is subdivided with a relatively large frame it becomes obvious that such a generalisation is sweeping and that there exists noradrenergic heterogeniety in OCD. This explains the observation of a normal to augmented growth hormone response to OCD observed by Hollander (1989). What is perhaps most interesting is the observation that pure obsessionals tend to have a more down regulated noradrenergic system as compared to the compulsives.

When Zohar *et al.* (1987, 1988) administered m-chlorophenylpiperazine to OCD subjects they used to try and stimulate the environment in which such obsessions occur. However it is well recognised that such a situation could be stressful and lead to noradrenergic stimunlation. When Khanna *et al.* (1989) repeated this study without invoking such stressful environments they were not able to observe exacerbations in obsessive-compulsive psychopathology. Even when this agent is given intravenously the same observation is made

(Charney *et al.*, 1988). It therefore seems reasonable to presume that a 5HT hypersensitive state is a precondition for the development of the OCD, but it on its own may not be sufficient. What is perhaps required in addition either a state wherein exogenously produced stress causes noradrenergic release, or there needs to be an endogenous noradrenergic state which produces such psychopathology (Fig. 5).

The interesting differentiation between obsessionals and compulsives assume great therapeutic importance, as behavioural lines of management are far more successful for compulsive (Marks, 1987) than for pure obsessionals. Perhaps these later subjects require correction of their noradrenergic state to facilitate clinical recovery.

At a methodological plane, it appears from this investigation that the ACTH response to clonidine is a fairly sensitive marker of noradrenergic function. However it is obvious that a study on OCD, in which noradrenergic dysfunction is only now being proposed, would not be sufficient to support this. Nevertheless the rapid rise in ACTH after clonidine administration makes it an important marker for such an approach.

This study aims to integrate the serotonergic biology of OCD with noradrenergic dysfunction which can be produced by a host of conditions, such as stress. It may well help in linking behavioural and bilological approaches to the undertaking of OCD and its subsequent therapy. However it would be perhaps too early and too simplistic to accept this model as being final. It needs replication and a greater understanding of the differentiation of pure obsessionals and compulsives. It does not rule out the possibility of involvement of other neurotransmitters and behavioural models, but aims at opening the horizon regarding the undertaking of the very personally distressful obsessive compulsive state.

REFERENCE

American Psychiatric Association (1980). Diagnostic and Statistical Manual for mental disorders, 3rd edition. American Psychaitric press, Inc., Washington.

Amesterdam, J.D.; Mlaslin, G.; Skolnick, B.; Berwish, N. and Winokur, A (1989). Multiple hormone responses to clonidine administration in depressed patients and healthy volunteers. Biological Psychiatry, 26, 265-278.

Bennett, G. and Whitehead, S.A. (1983). Mammalian neuroendocrinology. Billing and Sons Ltd., Kent.

Charney, D.S.; Goodman, D.K.; Price, L.H.; Woods, S.W.; Rasmussen, S.A. and Heninger, G.R. (1988). Serotonin function in Obsessive Compulsive Disorder. A comparison of the effects of tryptophan and m-chlorophenylpiperazine in patients and healthy subjects. Arcives of General Psychiatry, 45, 177-185.

Cooper, J.E. (1970). Leyton's Obsessional Inventory. Psychological Medicine, 1, 48-64.

Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurdsurgery and Psychiatry, 23, 56-62.

Hollander, E. (1989). Neurobiology of obsessive compulsive disorder. Presented at World Associaation of Biological Psychiatry Regional symposium on Biological aspects of non-psychotic disorders. Jerusalem.

Hollander, E.; Fay, M.; Cohen, B.; Campeas, R.; Gorman, J.M. and Liebowitz, M.R. (1988). Serotonergic and noradrenergic sensitivity in obsessive and compulsive disorder. American Journal of Psychiatry, 145, 1015-1017.

Hollander, E.; Fay, M. and Liebowitz, M.R. (1988). Clonidine and clomipramine in obsessive and compulsive disorder. American Journal of Psychiatry, 145, 388-389.

Kahn, R.S. and Wetzler, S. (1991). m-chlorophenylpiperazine as a probe of serotonin function. Biological Psychiatry, 30, 1139-1166.

Khanna, S. (1988). Biological correlates of obsessive and compulsive disorder. Indian Journal of Psychiatry, 11, 59-68.

Khanna, S. (1990). An open trial of clonidine in obsessive and compulsive disorder. Presented at XVI Conference of Collegium Internationale Neuro-psycho-Pharmacoligicum, Kyoto.

Khanna, S. (1992). Biology of Obsessive and compulsive disorder. In : Vyas, J. and Ahuja, N. (Eds.) Recent Advances in Psychiatry. I in press).

Khanna, S.; Mukundan, C.R. and Channabasavanna, S.M. (1987). Obsessive compulsive disorder : Is it a problem of complex motor programming ? Indian Journal of Psychiatry, 29, 47-54.

Khanna, S.; Reddy, P.L.; Subhash, M.N.; Rao, B.S.S. and Channabasavanna, S.M. (1989). Oral m-CPP in obsessive compulsive disorder. Presented at VIII World Congres of Psychiatry, Athens.

Khanna, S.; Reddy, P.L.; Subhash, M.N.; Rao, B.S.S. and Channabasavanna, S.M. (1989). Multiple endocrine rsponse to clonidine in normals. Neuroendocrine Letters, 4, 323.

Knesevich, J.W. (1982). Sucessful treatment of obsessive compulsive disorder with clonidine hydrochlorise. American Journal of Psychiatry, 139, 364-365.

Lee, M.A.; Cameron, O.G.; Gurguis, G.N.M.; Glitz, D.; Smith, C.B.; Hariharan, M.; Abelson, J.L. and Curtis, G.C. (1990). Alpha2 adrenoreceptor status in obsessive compulsive disorder. Biological Psychiatry, 27, 1083-1093.

Lipsedge, M.S and Prothero, W. (1987). Clonidine and clomipramine in obsessive compulsive disorder. American Journal of Psychiatry, 144, 965-966.

Marks, I.M. (1987). Fears, phobias and rituals. Oxford University Press, London.

Murphy, D.L.; Zohar, J.; Benkelfat, C.; Pato, M.T.; Pigott, T.A. and Insel, T.R. (1989). Obsessive Compulsive disorder as a 5TH subsystem related behavioural disorder. British Journal of Psychiatry, 155 (Suppl 8), 15-24.

Myers, J.K.; Weissman, M.M.; Tischler, G.L.; Holzer, C.E.; Leaf, P.J.; Orvaschel, H.; Antony, J.C.; Boyd, J.H.; Burke, J.D.; Kramer, M. and Stolzman, R. (1984). Six month prevalence of psychiatric disorders in three communities 1980-1992. Arcives of General Psychiatry, 41, 959-967.

Rao, A.S. and Rao, I.V.L.N. (1988). Sucessful treatment of obsessive compulsive disorder with clonidine. Andhra Pradesh Journal of Psychological Medicine, 1, 116-118.

Siever, L.J. and Uhde, T.W. (1984). New studies and perspectives on the noradrenergic receptor system in depression. Biological Psychiatyr, 19, 131-156.

Zohar, J. and Insel, T.R. (1987). Obsessive compulsive disorder : Psychobiological approaches to diagnosis, Treatment and Psycho-pathology. Biological Psychiatry, 22, 667-687.

Zohar, J.; Mueller, E.A.; Insel, T.R.; Zohar-Kadouch, R.C. and Murphy, D.L. (1987). Serotoneergic responssivity in obsesive compulsive disorder. Archives of General Psychiatry, 44, 946-951.

Zohar, J; Insel, T.R.; Zohar-Kadouch, R.C.; Hill, J.L. and Murphy, D.L. (1988). Serotonergic responsivity in obsessive compulsive disorder : effects of chronic clomipramine treatment. Archives of General Psychiatry, 45, 167-172.