Research article
Ερευνητική εργασία

Agomelatine augmentation in obsessive compulsive disorder: A preliminary report

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Obsessive-compulsive disorder (OCD) is often the anxiety disorder that affects approximately 2% of the population. This disorder is associated with significant morbidity and dysfunction, and is included in the World Health Organization list of the ten most disabling medical illnesses. The therapeutic response of patients with OCD is relatively poor compared with that of other mental disorders. Pharmacological interventions for OCD have focused on modulating primarily serotonin function and secondarily dopamine neurotransmission. Augmentation treatment has been the subject of several studies in treatment-resistant obsessive compulsive disorder (OCD). We hypothesized that medications with a dual action on the melatoninergic and serotoninergic systems may be of use in treatment-resistant OCD. In this open label study we investigated the efficacy and safety of agomelatine augmentation in treatment-resistant OCD. Twelve patients, aged 18–50, fulfilling OCD criteria, having failed to respond to adequate treatment with a Serotonine Reuptake Inhibitor for at least 16 weeks, were assigned to receive agomelatine augmentation. Subjects were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and were screened for treatment-emergent side effects at baseline and week 16 of treatment. We excluded patients with comorbid psychopathology, serious medical comorbidity, current or past history of substance abuse and severe personality disorders as well as patients receiving psychotherapy in addition to psychopharmacological treatment. Agomelatine augmentation lead to net improvement in Y-BOCS and its obsession and compulsion subscales after 16 weeks of treatment (all $p<0.005$). Agomelatine augmentation was well-tolerated and none of the patients dropped-out. Treatment-related adverse events were recorded as follows: (n, %): nausea: 1 (8.3%), headache 4 (33.3%), dizziness: 3 (25%) and somnolence: 2 (16.7%). The present case series study has several limitations due to its open-label design and the absence of a placebo or active control group. The small number of patients further limits the impact of our findings. The present case series study

showed that a 16 week add-on treatment with agomelatine, achieved on average a 25% improvement in Y-BOCS in refractory to treatment OCD patients; side effects were mild, and none of the patients dropped out throughout the 16-week study period. Agomelatine could be efficacious and well tolerated as an augmenting agent in refractory to treatment OCD. The unique pharmacological profile of agomelatine and its dual action on serotoninergic and melatoninergic receptors may be of interest in this difficult-to-treat illness. Further controlled studies are warranted to explore the efficacy of agomelatine, as well as the potential role of circadian rhythm modulation both in the pathophysiology and treatment of OCD.

Key words: Agomelatine, augmentation, obsessive compulsive disorder.

Introduction

Obsessive-compulsive disorder (OCD) is often a debilitating anxiety disorder that affects approximately 2% of the population.[1]

Characterized by recurrent anxiety-laden thoughts, images or impulses (obsessions) and accompanying behavioral or mental rituals (compulsions) meant to abate anxiety, the disorder is associated with significant morbidity and dysfunction, and is included in the World Health Organization list of the ten most disabling medical illnesses.[2]

The therapeutic response of patients with OCD is relatively poor compared with that of other mental disorders. Although symptom reduction by 20–40% is considered as satisfactory in most treatment trials, many responders remain markedly symptomatic;[3] consequently, novel therapeutic strategies are urgently needed.

Pharmacological interventions for OCD have focused on modulating primarily serotonin function and secondarily dopamine neurotransmission.[4] Medications that increase serotoninergic neurotransmission constitute the cornerstone of OCD pharmacotherapy.[5] However, 40–60% of OCD patients do not respond adequately to therapy with serotonin reuptake inhibitors (SRIs), and an even greater proportion of patients fail to achieve complete remission of their symptoms and therefore continue to experience significant impairment from their residual OCD symptoms.[3] Augmentation strategies with antipsychotics, buspirone and lithium are common practice either in patients with treatment-refractory OCD or in cases with psychiatric comorbidity, which is relatively common in OCD.[6]

Recent clinical studies have implicated also melatoninergic dysfunction in the pathophysiology of OCD, and preliminary data support the usefulness of augmentation with a melatoninergic agent in treatment-resistant OCD patients; consequently, investigators underline the need for more and larger trials.

We hypothesized that medications which resynchronize and attenuate melatoninergic activity (with a concurrent role in serotonin function) may be of benefit in the treatment of SRI-resistant OCD.[7–9] The objective of this open label case series study was to determine the efficacy and safety of agomelatine augmentation in treatment-resistant OCD.

Material and method

Over a calendar year we followed closely twelve outpatients (mean age±SD: 28.4±6.5 years) with treatment-resistant OCD. To be included in this case series the patients had to be 18–50 y.o., fulfilling the DSM-IV-TR OCD criteria, having failed to respond to adequate treatment with a SRI (SSRIs, venlafaxine or clomipramine) for at least 16 weeks. Moreover, they all had to show less than 25% score reduction on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) following SRI treatment and a score ≥18 on the Y-BOCS.[10] We excluded patients with comorbid psychopathology, serious medical comorbidity, current or past history of substance abuse and severe personality disorders as well as patients receiving psychotherapy in addition to psychopharmacological treatment. Evaluation included the Mini-International Neuropsychiatric Interview (used to document the presence of OCD and comorbid conditions), the Y-BOCS (used for the assessment of severity of OCD symptoms and treatment response) and the Systematic Assessment for Treatment Emergent Events scale (SAFTEE; to assess safety and tolerability of treatment);[11] spontaneous reports or observed adverse events were recorded regarding time of onset,

duration and severity. All the patients underwent a routine laboratory screening according to the SPC and clinical side effects screening test. The study was approved by the in-hospital human subjects ethics board and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000; written informed consent was obtained from all the included patients.

Agomelatine 25 mg/day with an increase to 50 mg/day after two weeks was added to the existing OCD regimen. Assessments were performed at baseline and after 16 weeks of treatment (end of the study).

Statistical analysis

The Wilcoxon signed rank sum test was applied to compare baseline and end Y-BOCS scores using SPSS v. 17 (SPSS Inc, Chicago, IL, USA).

Results

Mean score ± SD on the Y-BOCS and its two subscales as well as distribution of scores at baseline and after 16 weeks of treatment are shown on table 1. Agomelatine augmentation lead to net improvement in Y-BOCS and its obsession and compulsion subscales after 16 weeks of treatment (all $p<0.005$). Agomelatine augmentation was well-tolerated and none of the patients dropped-out. Treatment-related adverse events were recorded as follows: (n, %): nausea: 1 (8.3%), headache 4 (33.3%), dizziness: 3 (25%) and somnolence: 2 (16.7%).

Discussion

The present case series study showed that a 16 week add-on treatment with agomelatine, achieved on average a 25% improvement in Y-BOCS in refractory to treatment OCD patients; side effects were mild, and none of the patients dropped out throughout the 16-week study period.

Augmentation has been the subject of several studies on treatment-resistant OCD Augmentation strategies in obsessive-compulsive disorder.[12] In general, the addition of a low dosage antipsychotic to an SSRI should be considered if all other approaches have failed, i.e., attempts with various SSRIs and cognitive behavioural psychotherapy. Lithium, anticonvulsants, buspirone and ECT have been widely investigated, especially when comorbid conditions exist. Our study supplements and extends the findings of Fomaro et al[13] who demonstrated the efficacy of agomelatine monotherapy in a switch study in SRI-resistant OCD patients with comorbid anxiety and affective disorders. In our study, OCD patients without comorbid psychiatric disorders were enrolled, with a relatively higher Y-BOCS score upon entering the trial.

Although agomelatine's efficacy in the treatment of major depressive disorder has been widely investigated, there are limited data regarding its potential role in the management of OCD. Agomelatine's mode of action through 5-HT_2C modulation and subsequent norepinephrine and dopamine firing disinhibition at the prefrontal cortex, as well as the influence of MT_1 and MT_2 agonism on circadian rhythms, might suggest a potential role of agomelatine in the management of anxiety disorders, including OCD.[7,13] In addition, side effects associated with agomelatine augmentation, i.e., dizziness, headache, somnolence and nausea, were mild, subsided within a few days and none of the participants dropped out of the study.

Limitations

The present case series study has several limitations due to its open-label design and the absence of a placebo or active control group. The small number of patients further limits the impact of our findings. Moreover, the duration of a therapeutic trial with a SRI, prior to augmentation with agomelatine, should be of an adequate dose and duration, since the response to anti-OCD medications is relatively slow, while there is evidence that patients continue to improve even after a 12-week period. To tackle this point in our study, we ensured that all participants received antidepressants at an adequate dose for at least 4 months prior to entry.

In conclusion, this study suggests that agomelatine as an add-on agent could be efficacious and well-tolerated in OCD patients refractory to treatment. The unique pharmacological profile of agomelatine and its dual action on serotoninergic and melatoninergic receptors may be of interest in this difficult-to-treat illness. Further controlled studies are warranted to explore the efficacy of agomelatine, as well as the potential significance of circadian rhythm modulation in both the pathophysiology and treatment of OCD.

Table 1. Efficacy result for twelve patients with obsessive-compulsive disorder who received augmentation as add-on therapy and completed the trial.

Patient Sex Age	*Antidepressant and dose (mg/day)*	*Baseline YBOCS total*	*Endpoint YBOCS total*	*Change YBOCS total (%)*	*Baseline YBOCS Obsession scale*	*Endpoint YBOCS Obsession scale*	*Change (%) YBOCS Obsession scale*	*Baseline YBOCS compulsion scale*	*Endpoint YBOCS compulsion scale*	*Change (%) YBOCS compulsion scale*
1 M 27	Citalopram 80	25	18	28	12	10	16.6	13	8	38.4
2 F 24	Flyvoxamine 300	23	19	17.3	13	11	15.3	10	8	20
3 F 36	Citalopram 80	24	20	16.6	9	8	11.1	15	12	20
4 M 28	Fluoxetine 60	21	11	45.6	12	5	58.3	9	6	33.3
5 M 29	Sertraline 250	22	12	45.4	11	7	36.3	11	5	54.5
6 M 44	Flyvoxamine 250	20	16	20	8	7	12.5	12	9	25
7 F 32	Venlafaxine 300	20	18	10	12	12	0	8	6	25
8 M 19	Fluvoxamine 300	21	20	4.7	11	11	0	10	9	10
9 M 25	Paroxetine 60	24	15	37.5	14	8	42.8	10	7	30
10 M 26	Venlafaxine 375	22	14	36.3	10	6	40	12	8	33.3
11 M 28	Sertraline 300	20	19	5	12	12	0	8	7	12.5
12 M 23	Fluoxetine 60	21	13	33.3	13	6	53.4	8	7	12.5
				(24.9%)			23.8%			26.2%
	Mean±SD	21±1.7	16.2±3.1		11.4±1.7	8.5±2.5		10.5±2.1	7.6±1.8	
	p	0.002			0.007			0.002		

M: male, F: female

Ενισχυτική θεραπεία με αγομελατίνη σε ανθεκτική ιδεοψυχαναγκαστική διαταραχή: Προκαταρκτική μελέτη

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Η ιδεοψυχαναγκαστική διαταραχή είναι συχνά η αγχώδης διαταραχή που επηρεάζει το 2% του πληθυσμού. Η διαταραχή αυτή συνδέεται με σημαντική νοσηρότητα και δυσλειτουργία, και περιλαμβάνεται από τη Παγκόσμια Οργάνωση Υγείας στη λίστα των δέκα ασθενειών που καθιστούν περισσότερο από τις υπόλοιπες ανίκανο τον ασθενή. Η θεραπευτική ανταπόκριση των ασθενών με ιδεοψυχαναγκαστική διαταραχή είναι σχετικά φτωχή σε σύγκριση με εκείνη των άλλων ψυχικών διαταραχών. Οι φαρμακολογικές παρεμβάσεις για την ιδεοψυχαναγκαστική διαταραχή έχουν επικεντρωθεί κυρίως στη λειτουργία και δράση της σεροτονίνης, και δευτερευόντως στη νευροδιαβίβαση της ντοπαμίνης. Η ενίσχυση της ανθεκτικής θεραπείας της ιδεοψυχαναγκαστικής διαταραχής έχει γίνει αντικείμενο μελέτης αρκετών ερευνών. Ως υπόθεση θεωρούμε ότι τα φάρμακα με διπλή δράση στο σεροτονινεργικό καθώς και στο μελατονινεργικό σύστημα μπορούν να χρησιμοποιηθούν στους ανθεκτικούς στη θεραπεία ιδεοψυχαναγκαστικούς ασθενείς. Σε αυτή τη μελέτη ελέγχουμε την αποτελεσματικότητα και την ασφάλεια της αγομελατίνης ως ενίσχυση της θεραπείας ανθεκτικών ιδεοψυχαναγκαστικών ατόμων. Το δείγμα περιελάμβανε 12 ασθενείς, ηλικίας 18–50 ετών, που πληρούσαν τα κριτήρια της ιδεοψυχαναγκαστικής διαταραχής, οι οποίοι δεν ανταποκρίθηκαν σε επαρκή θεραπεία με αναστολείς επαναπρόσληψης σεροτονίνης για ένα διάστημα τουλάχιστον 16 εβδομάδων και έλαβαν ως ενίσχυση της θεραπείας τους αγομελατίνη. Οι ασθενείς αξιολογήθηκαν με τη Yale-Brown Ιδεοψυχαναγκαστική Κλίμακα (Y-BOCS), και επιπλέον έγινε έλεγχος για παρενέργειες του φαρμάκου στην έναρξη της χορήγησης και στη 16η εβδομάδα της θεραπείας. Αποκλείσθηκαν ασθενείς με συννοσηρότητα είτε με άλλη ψυχική νόσο είτε με άλλη σοβαρή σωματική ασθένεια, ασθενείς με ιστορικό κατάχρησης ουσιών ή και κατάχρηση ουσιών κατά την περίοδο της έρευνας, ασθενείς με σοβαρή διαταραχή προσωπικότητας, καθώς και εκείνοι που πέρα από φαρμακευτική αγωγή είχαν τεθεί και σε ψυχοθεραπεία. Η ενίσχυση της θεραπείας με αγομελατίνη οδήγησε σε μια ξεκάθαρη βελτίωση στη Y-BOCS κλίμακα και τις υποκλίμακες αυτής που αφορούν τις ιδεοληψίες και τους καταναγκασμούς μετά τις 16 εβδομάδες θεραπείας (όλες $p<0,005$). Η ενίσχυση της θεραπείας με αγομελατίνη ήταν καλά ανεκτή και κανένας ασθενής από το δείγμα δεν εγκατέλειψε τη μελέτη. Οι παρενέργειες σχετιζόμενες με τη θεραπεία καταγράφηκαν ως εξής (n, %): ναυτία 1 (8,3%), κεφαλαλγία 4 (33,3%), ζάλη 3 (25%) και υπνηλία 2 (16,7%). Η παρούσα μελέτη έχει διαφόρους περιορισμούς λόγω του σχεδιασμού της και της έλλειψης εικονικού φαρμάκου ή ομάδας ελέγχου. Ο μικρός αριθμός των ασθενών επίσης περιορίζει τη βαρύτητα των ευρημάτων μας. Η παρούσα μελέτη κατέδειξε ότι η ενισχυτική θεραπεία 16 εβδομάδων με αγομελατίνη οδήγησε σε βελτίωση κατά 25% στους ανθεκτικούς ιδεοψυχαναγκαστικούς ασθενείς. Οι ανεπιθύμητες ενέργειες ήταν ήπιες και κανείς από τους ασθενείς δεν εγκατέλειψε τη μελέτη. Η αγομελατίνη πιθανώς θα μπορούσε να είναι αποτελεσματική και καλά ανεκτή ως προσθήκη σε ανθεκτική στη θεραπεία ιδεοψυχαναγκαστική διαταραχή. Το ιδιαίτερο φαρμακολογικό προφίλ της αγομελατίνης με τη διπλή δράση στους σεροτονινεργικούς και μελατονινεργικούς υποδοχείς μπορεί να χρησιμεύσει στις περιπτώσεις αυτές. Περαιτέρω μελέτες είναι αναγκαίες προκειμένου να διερευνηθεί ο ρόλος της αγομελατίνης τόσο στην παθοφυσιολογία όσο και στη θεραπεία της ιδεοψυχαναγκαστικής διαταραχής.

Λέξεις ευρετηρίου: Αγομελατίνη, ενίσχυση θεραπείας, ιδεοψυχαναγκαστική διαταραχή.

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