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RESEARCH PAPER

Randomised controlled trial of escitalopram for cervical dystonia with dystonic jerks/tremor

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ABSTRACT

Objective Trials for additional or alternative treatments for cervical dystonia (CD) are scarce since the introduction of botulinum neurotoxin (BoNT). We performed the first trial to investigate whether dystonic jerks/tremor in patients with CD respond to the selective serotonin reuptake inhibitor (SSRI) escitalopram.

Methods In a randomised, double-blind, crossover trial, patients with CD received escitalopram and placebo for 6 weeks. Treatment with BoNT was continued, and scores on rating scales regarding dystonia, psychiatric symptoms and quality of life (QoL) were compared. Primary endpoint was the proportion of patients that improved at least one point on the Clinical Global Impression Scale for jerks/tremor scored by independent physicians with experience in movement disorders.

Results Fifty-threepatients were included. In the escitalopram period, 14/49 patients (29%) improved on severity of jerks/tremor versus 11/48 patients (23%) in the placebo period (P=0.77). There were no significant differences between baseline and after treatment with escitalopram or placebo on severity of dystonia or jerks/tremor. Psychiatric symptoms and QoL improved significantly in both periods compared with baseline. There were no significant differences between treatment with escitalopram and placebo for dystonia, psychiatric or QoL rating scales. During treatment with escitalopram, patients experienced slightly more adverse events, but no serious adverse events occurred.

Conclusion In this innovative trial, no add-on effect of escitalopram for treatment of CD with jerks was found on motor or psychiatric symptoms. However, we also did not find a reason to withhold patients treatment with SSRIs for depression and anxiety, which are common in dystonia.

Trial registration number NTR2178.

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INTRODUCTION

Cervical dystonia (CD) is the most frequent variant of idiopathic focal dystonia,[1] and approximately 50% of patients display jerks (myoclonus) or head tremor.[2] Jerks and tremor are fast movements in contrast to phasic or mobile dystonia that consist of slower movements. Many patients with CD suffer from depressive symptoms and anxiety, with a lifetime prevalence of 40%–70%.[3] CD has a serious impact on quality of life that is mainly determined by depressive symptoms.[4] Botulinum neurotoxin (BoNT) injections in the affected muscles are an effective therapy for dystonic posturing and pain in CD.[5] Unfortunately, jerks and tremor can be troublesome, do not respond so well and no alternative treatments are available.[6]

The dopamine system has been implicated in the pathophysiology of dystonia. Using molecular imaging, abnormalities were found in dopaminergic signalling.[7 8] We showed that lower striatal dopamine $D_{2/3}$ receptor and dopamine transporter (DAT) binding in CD is associated with depressive symptoms.[8] We also found a clear trend towards lower serotonin transporter (SERT) binding in CD, particularly in patients with psychiatric symptoms. Interestingly, we also detected a different correlation between striatal DAT and extrastriatal SERT binding in CD patients with and without jerks/tremor.[9] Serotonin plays an important role in major depression and anxiety disorders and treatment with selective serotonin receptor inhibitors (SSRIs) is effective for both.[10] Abnormalities of the serotonergic system, which lead to a decrease in serotonin level, have been described in myoclonus. However, an altered serotonin level was detected in patients with Parkinson's disease with rest tremor compared with those without tremor.[11]

Neurotransmitter imbalance (especially increased levels of dopamine and decreased levels of serotonin) has been suggested to play a role in the pathophysiology of dystonia.[12] Medication restoring this balance might be useful in treating all symptoms of CD, including the psychiatric symptoms.[12] In the past, tetrabenazin, which blocks the vesicular monoamine transporter in dopaminergic neurons (and consequently the reuptake of dopamine in vesicles), was proven to be effective on motor symptoms. Currently, it is not frequently used because of significant side effects due to effects on other neurotransmitter systems such as serotonin and norepinephrine.[13] As suggested in a recent review, an SSRI to raise serotonin levels might be effective in CD.[12] We hypothesised that escitalopram would reduce tremor and jerks and dystonic and psychiatric symptoms in patients with CD.

MATERIAL AND METHODS

Subjects

We included 64 patients between 35 years and 80 years with idiopathic CD who regularly received BoNT injections from seven specialised outpatient clinics in the Netherlands between July 2010 and April 2014. Eleven patients did not suffer from jerks/tremor but served as controls for an imaging study using single-photon emission computed tomography (SPECT) imaging, and they were not included in the current study, resulting in 53 CD patients with jerks or tremor. Dystonia severity had to be stable for at least 1 year on the Tsui scale. Jerks or tremor had to be clearly visible at the outpatient clinic to consider a patient eligible. Exclusion criteria were (1) current or previous other neurological conditions, (2) treatment with deep brain stimulation (DBS), (3) use of SSRIs or other antidepressants in the past 20 weeks before inclusion or during the study, (4) symptomatic therapy for dystonia other than BoNT (including anticholinergics), (5) use of dopaminergic and serotonergic drugs, (6) use of medication with a known interaction with escitalopram and (7) pregnancy or lactation. Patients with low dosages of benzodiazepines were eligible, as long as the dosage of the benzodiazepine was maintained stable during the study period. Patients were diagnosed with idiopathic CD by an experienced, movement disorder neurologist before starting BoNT treatment and neurological examination and, when indicated, additional tests (laboratory tests, genetic tests and CT or MRI scans) did not reveal inherited or acquired dystonia. The medication trial started the day patients received BoNT injections or a maximum of 7 days after BoNT administration (see below). BoNT dosage was kept stable during the study, and considering the crossover design, it was considered not to influence the results of the present study. This study was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent prior to inclusion in the study. The study is registered at the Dutch Trial Register (www.trialregister.nl; NTR2178).

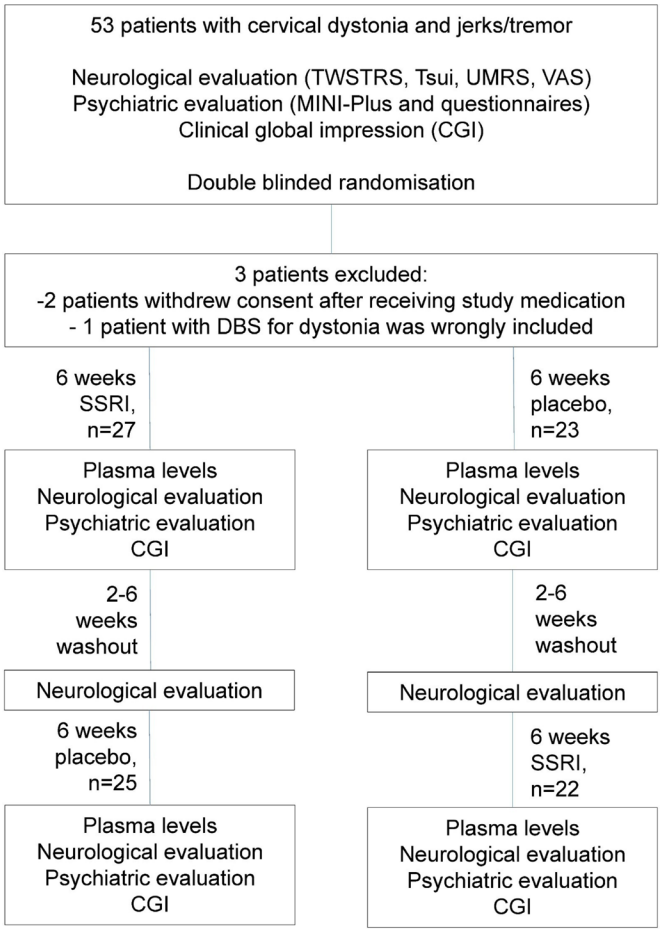

Figure 1 Flow chart of study. DBS, deep brain stimulation; MINI-Plus, MINI International Neuropsychiatric Interview Plus; SSRI, selective serotonin reuptake inhibitor; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; UMRS, Unified Myoclonic Rating Scale; VAS, visual analogue scale.

Experimental design and treatment

This study is a randomised, double-blind, crossover study. The flow chart in figure 1 shows an overview of the study. Patients were randomly assigned to first receive one of two treatment options: 10 mg of escitalopram or placebo once daily for the duration of 6 weeks. All medication was prepacked in neutral batches, and escitalopram and placebo tablets looked identical. Randomisation per block of 4 subjects in 1:1 ratio was based on a randomisation list that was created at the start of the study by an independent statistician, who also safeguarded the randomisation code. Block randomisation was used because part of these patients also participated in imaging studies, at baseline and after 6 weeks treatment with placebo or escitalopram, in which we wanted to balance the numbers of patients with and without jerks/tremor who used escitalopram or placebo. Participants and all study personnel were blinded for treatment allocation. Escitalopram was chosen because it has the highest affinity for the SERT and is the most selective SSRI.[14] Medication was handed out at the first study visit, after neurological and psychiatric symptoms were scored. Patients returned after 6 weeks, at which time the neurological and psychiatric examinations were repeated. Blood for analysis of plasma levels of escitalopram was withdrawn and stored at −20°C until analysis. Samples were analysed in batches of 10–20 samples using a validated Liquid chromatography–mass spectrometry (LC-MS/MS) method (range of detection 5–500 µg/L).[15] Results were given to the researchers after data collection was completed. Hereafter, a washout period of 2–6 weeks for the SSRI or placebo followed. The length of the washout period was determined by the BoNT treatment interval of the patient, which was 8–12 weeks. This visit was named '12 week visit' in all patients. The halftime of escitalopram is 30 hours, so a minimum period of 2 weeks was sufficient to wash out escitalopram completely. After the washout period, the interventions were switched. Previous to start of the second medication batch, a neurological examination was performed to assess severity of dystonia and jerks or tremor, similar to baseline assessment, since motor symptoms of CD can vary. We did not expect a large variation in psychiatric symptoms over the course of 12 weeks in a medication-free and BoNT-free condition and did not repeat the psychiatric examination at this point. The beginning of the intervention was again started within a week after BoNT injections. The neurological and psychiatric examinations were repeated after 6 weeks and blood for analysis of plasma levels was withdrawn. This visit was named '18 week visit' in all patients.

Scoring neurological and psychiatric symptoms

Patients received questionnaires to answer at home prior to their visits. We used the Yale-Brown Obsessive Compulsive Scale symptom checklist (Y-BOCS), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Liebowitz Social Anxiety Scale (LSAS). All these questionnaires score symptoms in the past week including the current day. We also used the Short Form

36 Health Survey (SF-36), to measure quality of life, and the Amsterdam Linear Disability Scale (ALDS). To assess self-reported severity of dystonia, we included the 10 cm visual analogue scale (VAS) both for current and optimal situation under BoNT treatment in which higher scores indicate more severe symptoms[16] and the Clinical Global Impression Scale (CGI).[17] The latter is a questionnaire with two questions both with a seven-point rating scale, in which higher scores indicate more severe symptoms, that was used to assess the severity of dystonia, jerks/tremor and psychiatric symptoms. The CGI was scored by both patients and clinicians. During visits, patients were systematically neurologically examined. Neurological examination was videotaped, and each video was scored by two experienced clinicians independent of the research team (CCSD, JMD, JHTMK, SMvdS, MatS, MarS and MAJT). The raters received four videos of the neurological examination taken at baseline, 6 weeks, 12 weeks and 18 weeks. The videos were supplied in random order, and the raters were blinded for the moment the video was taken. Clinicians scored the dystonic symptoms on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[18] and the Tsui scale for severity of dystonia.[19] Jerks/tremor were scored with the Unified Myoclonic Rating Scale (UMRS).[20] The CGI was used to score dystonia and jerks/tremor by the video-raters. After all videos of each subject were scored, physicians received the correct order for the videos and scored the CGI improvement for dystonia and jerks/tremor. Interobserver reliability was assessed in a subset of patients and was good (>80) for Tsui and TWSTRS and reasonable for UMRS (0.73).[8] The psychiatric interview was performed by trained investigators (EZ and YEMD) and consisted of the MINI International Neuropsychiatric Interview Plus (MINI-Plus), Montgomery-Åsberg Depression Rating Scale (MADRS) and the Y-BOCS Severity Scale. The CGI was also used to score overall severity for psychiatric symptoms by the interviewer based on the interview and scores from the questionnaires.

Outcome assessments

Primary endpoint was the proportion of patients that improved at least 1 point on the CGI scale for severity of jerks/tremor scored by the video-raters measured before and after 6 weeks of treatment with escitalopram compared with 6 weeks of treatment with placebo. Secondary endpoints were the proportion of patients with psychiatric comorbidity, the change on the CGI scale for severity of psychiatric symptoms, jerks and dystonia after treatment both scored by the patients as well as by the video-raters, the change on other neurological and psychiatric scales and the number and type of adverse events during treatment.

Statistical analysis

We assumed that 20% of patients will improve at least 1 point on CGI for severity of jerks during placebo treatment, since in previous BoNT trials for CD, placebo effect was between 15% and 35%.[21 22] We predefined a clinical relevant difference as a proportion of patients of 50% that improve at least 1 point on the CGI during escitalopram use. Using Fisher's exact test with a 0.05 two-sided significance level, we calculated that a sample size of 44 patients would have 80% power to detect this difference. We anticipated 20% drop-outs and therefore included 53 patients.

After testing for normality, McNemar's test was used to calculate our primary endpoint and other binary endpoints. Scores on neurological and psychiatric scales were tested for normality before formal comparison. Based on that test either parametric (paired samples T-test) or non-parametric tests (Wilcoxon matched-pair signed-rank test) were used.

Potential treatment–period interactions were examined by comparing the delta scores (score after treatment–score before treatment) of both study arms (placebo first vs SSRI first) using McNemar's test. For the first treatment period, baseline scores were used as comparison and for the second treatment period 12-week scores were used. Analyses were carried out using SPSS V.23 and differences were considered significant at $P<0.05$.

Table 1 Baseline characteristics

Characteristic	Patients (n=50)
Age, y, mean (SD)	58.2±9.6
Male, n (%)	18 (36)
TWSTRS total score, mean±SD	35±9.2
TWSTRS severity score, median (IQR)	17 (15–19)
TWSTRS disability score, median (IQR)	10 (7–12.75)
TWSTRS pain score, median (IQR)	10 (6–12.75)
Tsui score, mean±SD	9.7±3.4
UMRS score, median (IQR)	13.5 (9–22.25)
VAS score now, median (IQR)	7 (5–8)
VAS score optimal BoNT effect, median (IQR)	3.5 (2–6)
MINI DSM-IV diagnosis, n (%)	22 (44)
MADRS score, median (IQR)	3.5 (1.8–9)
BDI score, median (IQR)	6 (3–10)
BAI score, median (IQR)	7.5 (4.8–13)
LSAS score, median (IQR)	26 (7–46.3)
Y-BOCS score, median (IQR)	2 (0–8.5)
SF-36, total score, median (IQR)	68 (50.8–78.3)
ALDS, theta score, median (IQR)	3.58 (3.0–3.6)
ALDS, total score, median (IQR)	89.5 (88.7–89.5)
CGI severity patient dystonia, median (IQR)	5 (4–6)
CGI severity patient jerks, median (IQR)	4 (3–6)
CGI severity patient psychiatry, median (IQR)	2 (1–4)
CGI severity physician dystonia, median (IQR)	3 (3–5)
CGI severity physician jerks, median (IQR)	3 (2–5)
CGI severity physician psychiatry, median (IQR)	1 (1–3)

Results are depicted as mean±SD for normally distributed variables and as median (IQR) for non-normally distributed variables.
ALDS, Amsterdam Linear Disability Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BoNT, botulinum neurotoxin; CGI, Clinical Global Impression; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; LSAS, Liebowitz Social Anxiety Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MINI, MINI International Neuropsychiatric Interview; n, number; SF-36, Short Form 36; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; UMRS, Unified Myoclonic Rating Scale; VAS, visual analogue scale; y, year; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

RESULTS

Baseline

We included 53 patients with CD and jerks/tremor. Three patients were excluded shortly after randomisation: two withdrew consent before taking study medication, and one patient was wrongly included as he was treated with DBS for dystonia (see figure 1). Fifty patients received study medication and were analysed in a (modified) intention-to-treat analysis. Baseline characteristics are depicted in table 1.

Almost half the patients (44%) fulfilled the criteria for a psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Multiple disorders in one patient were not uncommon. In 22 patients anxiety disorders were scored, social phobia (eight cases) and agoraphobia

Table 2 Scores after treatment

Characteristic	Escitalopram (n=49)	Placebo (n=48)	P value
CGI severity patient dystonia, median (IQR)	4 (3–5)	4 (3–5)	0.12
CGI severity patient jerks, median (IQR)	4 (3–4)	4 (3–5)	0.10
CGI severity patient psychiatry, median (IQR)	1 (1–2)	1 (1–2)	0.59
CGI severity physician dystonia, median (IQR)	3 (3–4)	3 (3–4.8)	0.03
CGI severity physician jerks, median (IQR)	3 (2–4.5)	3 (2–4)	0.14
CGI severity physician psychiatry, median (IQR)	1 (1–2)	1 (1–2)	0.54
CGI improvement patient dystonia, median (IQR)	4 (3–4)	4 (3–4)	0.84
CGI improvement patient jerks, median (IQR)	4 (3–4)	4 (3–4)	0.33
CGI improvement patient psychiatry, median (IQR)	4 (4–4)	4 (4–4)	0.37
CGI improvement physician dystonia, median (IQR)	4 (3–4)	4 (3.3–4)	0.74
CGI improvement physician jerks, median (IQR)	4 (3–4)	4 (3–4)	0.80
CGI improvement physician psychiatry, median (IQR)	4 (3–4)	4 (4–4)	0.12
TWSTRS total score, median (IQR)	34 (25.5–39.5)	35 (26–41)	0.70
TWSTRS severity score, median (IQR)	16 (13.8–19)	17 (14–19)	0.17
TWSTRS disability score, median (IQR)	10 (7–12)	10 (6–11)	0.71
TWSTRS pain score, median (IQR)	9 (0–12.5)	9 (4.3–11.8)	0.98
Tsui score, median (IQR)	8 (6–11)	9 (7–11)	0.48
UMRS score, median (IQR)	13 (7–20)	13 (7.3–19.8)	0.35
VAS score now, median (IQR)	6 (3.3–7)	6 (4–7)	0.27
VAS score optimal BoNT effect, median (IQR)	5 (2–6)	4 (3–6)	0.70
MINI DSM-IV diagnosis	9/49 (18%)	11/48 (23%)	1.0
MADRS score, median (IQR)	2 (0–4)	2 (0–5)	0.43
BDI score, median (IQR)	4 (1–8)	4 (1–6)	0.47
BAI score, median (IQR)	6 (2.3–8.8)	4.5 (3–11)	0.61
LSAS score, median (IQR)	13 (3.5–35)	13 (1–42)	0.60
Y-BOCS symptoms score, median (IQR)	0 (0–0)	0 (0–0)	0.21
Y-BOCS severity score, median (IQR)	0 (0–5.8)	0 (0–3.8)	0.06
ALDS theta score, median (IQR)	3.6 (3.1–3.6)	3.6 (3.1–3.6)	0.34
ALDS score, median (IQR)	89.5 (88.7–89.5)	89.5 (88.7–89.5)	0.37
SF-36, total score, median (IQR)	74 (54.5–82.5)	72.5 (55.3–83.8)	0.94

Depicted scores are after treatment scores for both treatment periods, respectively. ALDS, Amsterdam Linear Disability Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BoNT, botulinum neurotoxin; CGI, Clinical Global Impression; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; LSAS, Liebowitz Social Anxiety Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MINI, MINI International Neuropsychiatric Interview; SF-36, Short Form 36; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; UMRS, Unified Myoclonic Rating Scale; VAS, visual analogue scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 3 Adverse events

Characteristic	Escitalopram (n=49)	Placebo (n=48)
Total n of adverse events, n (n of patients)	78 (in 40 patients)	42 (in 29 patients)
AEs not related to medication, n (%)	4 (5)	3 (7)
AEs with an unlikely relation to medication, n (%)	8 (10)	11 (26)
AEs with a possible relation to medication, n (%)	40 (51)	25 (60)
AEs with a likely relation to medication, n (%)	25 (32)	1 (2)
AEs with a certain relation to medication, n (%)	1 (1)	2 (5)
Type of adverse event, n (% of patients)		
Gastrointestinal	18 (37)	6 (13)
Fatigue/low energy level	9 (18)	3 (6)
Pain (excluding neck pain)	6 (12)	7 (15)
Dizziness/light-headedness	5 (10)	2 (4)
Dry mouth	5 (10)	3 (6)
Sleep disturbances	4 (8)	1 (2)
More dystonia/jerks/neck pain	4 (8)	8 (17)
Sexual disturbances	4 (8)	0 (0)
Sweating	3 (6)	2 (4)
Psychiatric complaints	3 (6)	3 (6)
Other	16 (33)	7 (15)
Medication stopped, n (%)	4 (8)	0 (0)

AEs, adverse events; n,number.

(eight cases) being the most common. Thirteen patients had a mood disorder. Depressive episodes were the most common with seven cases. Five other disorders were seen: two cases of alcohol abuse, one case of alcohol dependence, one case of cannabis dependence and one case of body dysmorphic disorder. No patient fulfilled the criteria for obsessive–compulsive disorder. The high prevalence of agoraphobia and social phobia was also reflected in high scores on the LSAS. However, there was a large range in scores on the LSAS with 57% of patients scoring below 30 points (cut-off point for specific social anxiety disorder) and 11% scoring above 60 points (cut-off point for generalised social anxiety disorder). Patients ranked higher CGI scores for severity of dystonia and jerks/tremor than physicians.

Differences between escitalopram and placebo

The proportion of patients that improved at least one point on CGI severity of jerks/tremor according to the video-raters was 14/49 (29%) in the escitalopram and 11/48 (23%) in the placebo period (P=0.77). Twenty-four out of 48 (50%) patients experienced an improvement in CGI severity of jerks/tremor in the escitalopram period and 21/48 (44%) in the placebo period (P=0.80). There were no significant differences between escitalopram and placebo for the proportion of patients that improved on CGI severity of dystonia (physician 29% vs 19%, P=0.18; patients 58% vs 50%, P=0.39) or psychiatric symptoms (physician 31% vs 29%, P=1.0; patients 53% vs 55%, P=1.0). Median escitalopram plasma level was 11.5 µg/L (IQR 7.3–21.3 µg/L). (table 2)

There were no significant differences in scores on neurological, psychiatric and quality of life rating scales between treatment with escitalopram and placebo (table 2). The only exception was a slightly but significantly lower score on CGI severity for dystonia scored by the physician after treatment with escitalopram compared with treatment with placebo. However,

there was no difference in CGI improvement for dystonia scored by the physician or in CGI scores for dystonia scored by patients.

Differences baseline and treatment

There were no significant differences between the scores at baseline and at 6 weeks on the TWSTRS, Tsui or UMRS, either in the escitalopram period nor in the placebo period. Patients however gave themselves significantly lower scores on the VAS for severity of dystonia in both periods. There were statistically significant improvements on all psychiatric scales (MADRS, Y-BOCS, BDI, BAI and LSAS) after treatment with both escitalopram and placebo. There was no significant difference in scores on ALDS at baseline and after treatment with either escitalopram or placebo. Quality of life improved significantly both after treatment with escitalopram (P=0.006) as well as after treatment with placebo (P=0.001).

There were no significant treatment period interactions. There were small, non-significant differences in baseline measures on Tsui, VAS before BoNT injection and VAS for optimal BoNT effect and CGI severity for dystonia scored by physician between patients treated with escitalopram first and placebo first. On average, the patients treated with placebo first had less severe dystonia compared with patients treated with escitalopram first. There were no significant differences in TWSTRS, Tsui, UMRS or CGI severity for dystonia and jerks/tremor scored by the physician between baseline and the 12-week measurements.

Adverse events

Adverse events were most common in the escitalopram period (78 in the escitalopram vs 42 in the placebo period). No serious adverse events occurred in either period. Both in the escitalopram and the placebo period, six adverse events were considered severe by the patients. Most adverse events were considered moderate in severity (45/78 (58%) in escitalopram period, and 28/42 (67%) in placebo period. In the escitalopram period, the most commonly reported adverse events were gastrointestinal (mainly nausea), fatigue and pain in other body parts than the neck (mainly headache and muscle ache). Medication was discontinued because of adverse events in four patients in the escitalopram period. Reasons to discontinue medication were a combination of dry mouth, depressed feelings and loss of libido in one patient, fatigue and disturbed sensation in the legs in one patient, fatigue and depressed feelings in one patient and swelling of one eye, mouth and lips in one patient. In these patients adverse events disappeared after cessation of medication. (table 3)

DISCUSSION

We performed the first placebo-controlled, randomised controlled trial in dystonia since the introduction of BoNT. BoNT is a highly effective therapy for dystonic posturing, but head tremor and jerks are difficult to treat.[6] In the current study, we did not find a significant add-on effect of escitalopram for the treatment of dystonic jerks/tremor. In further exploratory analysis, there were also no indications of an add-on effect for dystonic posturing and psychiatric symptoms. SSRIs have been used to treat non-motor symptoms, such as fatigue and depression, in Parkinson's disease (PD). An effect has clearly been established for PD-related depression.[23] In PD-related fatigue, SSRIs did not prove to be effective, possibly due to loss of SERTs in the striatum and limbic system.[24] It is unclear whether loss of SERT plays a role in CD. We recently did not find a difference in SERT binding in midbrain/diencephalon between patients with CD and controls but were unable to examine the striatum and limbic system (unpublished work).

Notably, there were no signs of worsening of dystonia during escitalopram treatment. Case reports of dystonia developing after treatment with SSRIs have been published in the past. This makes physicians hesitant to prescribe SSRIs to patients already suffering from dystonia[25] while psychiatric symptoms are common in patients with CD. We show that there is no reason to be extra cautious to treat depression and anxiety with SSRIs in patients with CD. There is debate whether these psychiatric symptoms are a primary symptom of dystonia or secondary to a visible, debilitating and stigmatising disorder.[26] We show that, independent of study treatment with escitalopram or placebo, psychiatric symptoms are less prominent 6 weeks after BoNT injections. An improvement of psychiatric symptoms after treatment with BoNT has been reported previously in patients with dystonia.[4 27] This would be an argument that psychiatric complaints are (partly) caused by the dystonia. In fact, several studies have found that especially social phobia becomes present after the first dystonic complaints.[28 29] However, there are also several arguments that psychiatric complaints are part of the dystonia phenotype because they are more common in dystonia as compared with other chronic visible disorders[30] and often also start before the first symptoms of dystonia.[31 32] There may be an inert sensitivity to develop depressive episodes and anxiety, which is worsened by the motor symptoms of dystonia.

Another finding in this study is that none of the dystonia rating scales improved after 6 weeks of treatment despite that all patients received BoNT. As pointed out above, all patients had tremor or jerks that are more difficult to treat and thus these patients are likely to have a smaller treatment effect.[6] Furthermore, it is known that BoNT treatment effect reaches a steady state with less waxing and waning after years of treatment because of a well-established optimal individual treatment interval.[33] Inclusion in our study required treatment for at least 1 year, but most patients already received BoNT for many years. Another explanation could be that patients with the smallest treatment effect are most likely to participate in a trial for a new treatment.

The rating scales for psychiatric symptoms and quality of life in our study all improved after treatment with escitalopram as well as placebo. This has been described before as a result of BoNT injections[4 34] and could also be due to placebo effect. The placebo effect has been demonstrated in patients with major depression and may explain up to 75% of the therapeutic effect of antidepressants.[35] One of the neurotransmitters implicated in the placebo effect is dopamine.[36] In PD, an increase in striatal dopamine release was demonstrated immediately after administering a placebo while patients thought they received a dopamine agonist.[37] Dystonia is considered a hyperdopaminergic disorder, thus an inverse process where administering a placebo leads to a decrease in dopamine release, might cause the placebo effect. It would be interesting to examine the changes in concentration of neurotransmitters, especially dopamine and serotonin, in patients with CD after treatment with an SSRI or placebo as well as in patients with CD who did not receive medication but were followed up and evaluated intensively.

Our study has some limitations. First, our baseline incidence of psychiatric disorders is on the low end of that reported in literature (40%–70% in literature vs 44% in our cohort).[3 38] This is mainly due to the exclusion of patients that were currently using or had in the past 20 weeks used SSRIs or other antidepressants. Second, we chose a low dosage of escitalopram and treated patients for 6 weeks. Most trials in patients with major

depression use a treatment duration of 10–24 weeks, since treatment effect is usually more prominent after a longer treatment.[14] The hypothesis is that even though SSRIs induce an immediate increase of extracellular serotonin levels, slower adaptive neurochemical changes in the brain may be responsible for the positive treatment effect.[14] Also the plasma levels we measured were slightly lower than reported in the literature,[39] likely due to performing plasma analysis approximately 24 hours after last ingestion. In trials in patients with major depression clinical effect of SSRIsis hypothesised to be related to an 80% occupancy of the SERT which is reached at plasma levels of 5 ug/L.[40] We cannot exclude that the treatment duration in our study was too short and/or the dosage of escitalopram was too low to induce relevant (neuroadaptive) changes. Taking into account that the side effects were relatively mild, a longer prospective trial is safe to be performed.

In conclusion, we did not find an add-on effect of escitalopram for the treatment of CD with jerks/tremor (class I evidence), but it would be of interest to see if a longer treatment duration would be more effective. Because we did not find worsening of dystonia in patients with CD taking escitalopram, there seems to currently be no reason to withhold an approved therapy for depression and anxiety to patients with dystonia. We do feel that monitoring of long-term side effects is warranted.

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