D.7.2 Managing dopaminergic treatment in people who have developed impulse control disorder

Study details	Participants	Methods	Results	Comments
Full citation Okai,D., Askey-Jones,S., Samuel,M., O'Sullivan,S.S., Chaudhuri,K.R., Martin,A., Mack,R.J., Brown,R.G., David,A.S., Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers, Neurology.80 (9) (pp 792-799), 2013.Date of Publication: 26 Feb 2013., 792-799, 2013 Ref Id 308530 Country/ies where the study was carried out UK Study type RCT of CBT Aim of the study to test the effects of a novel CBT-based intervention delivered by a nurse therapist to patients with PD with clinically significant impulse control behaviours	Sample size N= 45 diagnosis of PD ; treatment n=28; waitlist n=16 Inclusion criteria diagnosis of PD according to UKBB criteria and associated ICB which had failed to remit despite measures taken by treating neurologist, including medication changes Exclusion criteria participants were excluded if did not meet inclusion criteria (n=11). standardized MMSE score <24, non english seakers, those without n identifiable carer able to participate in the trial	Details ICB screened using QUIP. following screening, ICD confirmed by clinical interview which made us of DSM IV criteria for pathological gambing, along with other criteri for the ICB Eligible consenting participants were randomly assigned to immediate treatment or 6 month waiting list randomization via random number tables held independently of those performnig the initial clinical assessment those randomized to treatment started immediate;y with intention to see people weekly for 12 sessions of treatment patients nd rather were aware of location following randomization Interventions treatment - CBT treatment manual was compiled during the pilot phase of the trial and informed by currently published treatment of ICDin general population adapted for a PD population, with additional components of communication and interpersonal relationships	Results demographics mean age; treatment = 59.3 years (8.1), control = 57.9 (9.5) male sex 19; treatment (67.9%), control 12 (70%) duration of PD; treatment 10.5 (6.0), control 8.8 (5.6) duration of ICB; treatment 4.4 (3.2), control 3.8 (4.6) Study data all patients completed t least one session in group and were completed in the analysis; 58% completed all and 88% completed at least 6 sessions No significant differences between groups based on demogrpahic and clinical characteristics, nor was there a difference in use of dopamine agonists or ledd. Total UPDRS scores were similar across treatment groups and remained stable over the course of treatment There was a significant effect with regard to changes in global levels of symptom severity using CGI as continuous measure with reduction in tmt group. 75% improved in treatment group compared to 29% in waitlist group The frequency and impact of ICB was significantly reduced over time in the treatment group. additionally there was an improvement in anxiety and depression in treatment group. GHQ-28 scores were significantly better in tmt gropou. GRIMS indicated no treatment effect on	**Overall Risk of Bias** 1. An appropriate method of randomization was used to allocate pts to treatment groups? yes - via independent random number table 2. There was adequate concealment of allocation no - not possible. patient, nurse, clinician qnd family all informed of allocation. The groups were comparable at baseline, including all major confounding and prognostic factors? yes 4. Comparison groups received same care apart from interventions. waitlist control received no care 5. Pts receiving care were kept blind to tmt allocation no - not possible 6. Individuals administering care were kept blind to tmt allocation no not

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Study dates published feb 2013 Source of funding Parkinson's UK		in relation to carers, executive dysfunction, and elements of case management. therapy was given by the same therapist supervied by a consultaant clinical psychologist. individual therapy supervision was provided once every 4 weeks amd included review to ensure manual adherence, fidelity, and quality therapy usually took place in patient' s homes although some sessions were done in clinic. notes were made on themes discussed in every session along with a record of number of treatment sessions attended, active withdrawals from treatment, and follow-up standard medical care all pts received information leaflets about treatments in PD and potental adverse effects those randomised to wait list recieived SMC and waited for 6 months before recieving intervention (results not reported here) SMC included ongoing review by patients treating physician, specialist nurse access, and potential referral to geriatrician	carers perception of the quality of their relationship with mean scores consistently rated as poor. No serious adverse outcomes were reported. Mean change (95% CI) scores are as follows: patient CGI: -0.8 (-1.2 to -0.5) NPI: -4.7 (-9.1 to -0.3) carer NPI distress: -3.0 (-5.6 to -0.3) patient: impulse behavioural scale: 4.7 (-5.8 to -2.5) work social adjustment scale: -3.6 (-6 to -1.3) GRIMS martital state questionnaire: 0.05 (-4 to 4.1) general health (GHQ): -3.8 (-5.6 to -2.0) BDI: -3.5 (-6.6 to 0.4) BAI: -1.8 (-5.4 to 1.8) carer GHQ: -1.5 (3.2 to 0.1) GRIMS: -2.3 (-5.7 to 1.3)	possible 7. All groups followed up for an equal length of time yes 8. Groups comparable for treatmen completion? yes 9. Grops were comparable with respect to avalilability of outcome data? yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes 12. Valid and reliable method was used to determine the outcome: yes well validated clinically meaningful outcome measures 13. Inves tigators were kept blind to participants exposure to the intervention yes 14. Investigator s were kept blind to other important confounding and prognostic factors: unclear **no serious risk of bias**

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		or neurologist if necessary. SMC did not preclude clinically necessary adjustment to medications		
Full citation Papay,K., Xie,S.X., Stern,M., Hurtig,H., Siderowf,A., Duda,J.E., Minger,J., Weintraub,D., 20141211, Naltrexone for impulse control disorders in Parkinson disease: a placebo-controlled study, Neurology, 83, 826-833, 2014 Ref Id 308584 Country/ies where the study was carried out USA Study type double-blind placebo controlled RCT Aim of the study To determine the efficacy and tolerability of naltrexone, an opioid antagonist, for the	Sample size N=50 randomised, N=45 completed study; n=26 received naltrexone; n=24 received placebo Inclusion criteria Participants aged 18 - 85 years with a diagnosis of ideopathic PD and compulsive gabling, sexual behaviours, or eating were enrolled into the study. ICD symptoms had to have begun after 1) PD onset and 2) initiation of DA treatment. Participants required to have been taking their current DA (ropinerole or pramexipole in all cases)for >6 months and on a stable dose for >1 month. Exclusion criteria	Details Following diagnostic criteria for ICD's was applied: DSM IV for PG; McElroy criteria for compulsive buying; Voon criteria for compulsive sexual behavior; DSM IV for compulsive binge eating disorder Study design: single-site 8 week 1:1 randomized double blind placebo controlled flexible dose 50-100mg/d participants randomly assigned via computer-generated variable block sizes (2 or 4 participants per block) with numbers sealed in opaque envelopes evaluated at baseline, week 2, week 4, week 6, week 8 at end of study baseline, week 4, week 8 visits in person, week 2 and week 6 conducted via telephone outcomes of interest: unstructured, clinician-completed CGIC chosen as primary outcome measure of change (range 1 - 7; 1 indicates very much improved, 7 indicates very	Results 45 patients completed study (90%): n=4 lost in naltrexone group, n = 1 lost after week 2 in placebo group demographics sex male % naltrexone =61.5, placebo 75 age yrs naltrexone = 61.3 (9.0) ; placebo 61.8 (8.2) MoCA naltrexone =26.9 (2.1); placebo 27.58(1.7) PD duration y naltrexone =7.35 (6.0); placebo 9.5 (7.2) Levodopa LEDD mg/d naltrexone 559.2 (410.7); placebo 594.7 (411.9) DA LEDD mg.d naltrexone 247.6 (130.9); placebo 330 (313.4) UPDRS motor naltrexone 19.5 (9.5); placebo 24.9 (10.7) baseline QUIP ICD core naltrexone 35.4 (17.9); placebo 30 (17.6) between group differences found in frequency of comorbid ICD's (50% in naltrexone vs 21% in placebo) and hisory of DBS (0% in naltrexone vs 17% in placebo): these variables entered as covariates in mixed effects model CGI-C no between-group difference for response with estimated response of 54,4% in naltrexone vs 33.1% in placebo: OR = 1.57, 95%CI: 0.47 to 5.23) at week 8	Overall Risk of Bias Other information findings of this study were negative for efficacy of naltrexone for treatment of ICD's using CGIC study lacked statistical precision to exclude important difference in response rates between naltresone and placebo using patient rated PD specific assessment of ICD - naltrexone treatment was associated with a decrease in ICD symptoms compared with placebo - may be easier to detect change in rating scale than in dichotomous measure of change

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treatment of ICD's in patients with PD Study dates Study dates not listed, published August 2014 Source of funding Study funded by clinical intervention award from the Michael J Fox foundation for Parkinson's research	Montreal cognitive assessment (MoCA) score of <20, active suicide ideation, history of DBS within the past year or onset of ICD symptoms temporarily related to DBS, active liver disease, alcohol or opiate dependence, overlapping psychiatric diagnoses, use of opiods for pain management,	much worse; score of 1 or 2 taken as reponsive, all other scores taken to be non responsive for this study) before study initiation, participants completed QUIP Parkinson's disease rating scale (QUIP-RS): score 0 -0 16 for each item (total of 0 - 64) where higher score = greater severity other items collected = geriatric depression inventory beck hopelessness scale Barratt impulsivity scale and tridimensional personality scales included as exploratory measures Interventions intervention = naltrexone: a competitive, nonselective opioid receptor antagonist. Currently efficacious in treatment of alcohol and opioid dependence . study details: For 1st 4 weeks, all participants administered naltrexone at 50 mg/d (or matching placebo). participants not in response (defined as a score of 1 or 2 on CGIC) at week 4 were increased to 100mg/d naltrexone or matching placebo for final 4 weeks	QUIP naltrexone led to greater decrease in QUIP ICD score over time compared to placebo at week 8 mean change naltrexone = (MC=14.92, 95%CI: 9.89 to 19.96); placebo group (MC= 7.55, 95%CI: 2.45 to 12.66); between group difference MD = -7.37 95%CI: 2.45 to 12.66 (nb 4 patients modified DA treatment during study period in naltrexone group - results still significant when these people removed from analysis at p<0.04) MID nominated as 7 points (0.5 SD) of change in the QUIP score over time in study completers:60% of naltrexone completers met this criteria clinical data no change in geriatric depression inventory (p=0.88) beck hopelessness (p=0.70) Baratt impulsivity scale (p=0.60) UPDRS motor scores changed from mean score of 19.5 (9.5) to 18.1 (8.6) in naltrexone and 24.9 (10.7) to 21.8 (11.1) in placebo group no between-group differences for change in UPDRS motor score over time adverse events 48 patients reported adverse events new onset nausea was common in naltrexone group (29.2% vs 0%, Fishers exact text p=0.0009) reported as mild to moderate intensity in all cases not associated with vomiting and did not lead to study discontinuation in any participants	because continuous measure provides more information and therefore better power to detect change

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		at study completion or termination, all study participants offered routine clinical care, including the option to take naltrexone	5 participants discontinued (4 naltrexone 1 placebo). None of these patients reported nausea or experienced any other adverse event likely to be due to study treatment other adverse events that occurred in >5% of patients that were more common in naltrexone group were dizziness (16.7% vs 4.2%) abd headaches (20.8% vs 16.7%) increase or decrease in blood pressure more common in placebo group (41.7& vs 25%)	
Full citation Thomas,A., Bonanni,L., Gambi,F., Di,Iorio A., Onofrj,M., 20100924, Pathological gambling in Parkinson disease is reduced by amantadine, Annals of Neurology, 68, 400-404, 2010 Ref Id 309188 Country/ies where the study was carried out Italy Study type double blind placebo-controlled crossover open extension study Aim of the study	Sample size N=17 Inclusion criteria patients with PD according to UKBB criteria with severe PG in the last 10 months that was no decreased by DA reduction or withdrawal or behavioural strategies. 17 patients were selected from a cohort of 1096 patients. PG identified according to DSM IV manual and south oaks gambling scale criteria. Exclusion criteria Patients affected by manic episodes or bipolar disorder and	Details PD symptoms evaluated with UPDRS, PD stage with H&Y scale, cognition with MMSE, and behavioural and mental functions with the NPI study design: 17 week double blind placebo controlled crossover 4 weeks baseline and 8 weeks amantadine/placebo crossover with 1 week washout and 4 weeks follow up PG was quantified by blind raters with gambling symptom assessment scale and the Yale-Brown Obsessive Compulsive scale for PG daily diaries assessed the time spent gambling and gambling cost in each day of the week. patients reports were double-checked with caregivers	Results demographics 13 male 2 female mean age 61.0 yrs (1.6) disease duration 52.4 months (7.8) H&Y stage 1.9 (0.2) LEDD (DA) mg, 1.2 (0.4) L-dopa dose 223.5 (49.2) duration of PG 7.1 months (0.4) results 5 patients dropped out because of side effect: confusion, orthostatic hypotension, insomnia (2 patients), and visual hallucinations. All were on amantadine branch. amantadine abolished daily expenditure, resolving PG in 7 patients and in 5 patients amantadine reduced Gambling on symptom assessment scale and yale brown obsessive compulsive scale, daily expenditure by 75%-90%, and time spent gambling amantadine effective in number of assessments, placebo was not effective in any area	**Overall Risk of Bias** 1. An appropriate method of randomization was used to allocate pts to treatment groups? NO: randomisation not clear 2. There was adequate concealment of allocation yes - double blind design 3. The groups were comparable at baseline, including all major confounding and prognostic factors? same groups 4. Comparison groups received same care apart from interventions yes 5. Pts receiving care were kept blind to

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<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>to investigate the possible efficacy of amantadine in the control of pathological gambling associated with PD

Study dates
Received Jan 2010, revised March, published March 2010

Source of funding
None listed</td>
<td>patients receiving antipsychotics or anticholinergics or previously exposed to amantadine were excluded from the study</td>
<td>assessments were performed twice during baseline period of 4 weeks (T1 and T2) and twice during follow up perdiod of 4 weeks, where only 12 patients recieved amantadine (T6, T7).
randomization at end of baseline period (T2) assigened amantadine/placebo with ratio 1:1
during crossover period, assessment done at T3 after 2 weeks of treatment,

Interventions
amantadine was administered as an add-on to the current antiparkinsonian medications, consisting of DA monotherapy, l-dopa monotherapy, L-dopa and DA therapy, entacapone, and rasagiline, unmodified throughout the study.
amantadine tablets were triturated and inserted into polymadine capsules; identical capsues containing agar gel were used as placebo
amantadine or placebo administered by a nurse unaware of patients assignments, with a titration schedule of 50mg twice daily fir 2 days and 100mg in the following 2 weeks., and was</td>
<td>comparison between amantadine and placebo revealed effect in favor of amantadine for G-SAS, Y-BOCS, and total gambling espentidute
G-SAS and Y-BOCS scores after 2 weeks of amantadine treatmen were reduced by 80% compared to baseline, whereas no changes occurred during the placebo treatment
differences between treatments in crossover study were statistically significant (G-SAS, F=522.9, p<0.0001; Y-BOCS, F=698.2, p<0001), regardless of whether dropped out patients were included
no carryover effect was observed (GSAS F=0.17, Y-BOCS F=1.59, both p>0.05)
no patient had side effects because of amantadine withdrawal.

<table>
<tr><td>% of salary expenditure</td><td>B</td><td>2.0 (0.2)</td></tr>
<tr><td></td><td>A</td><td>0.01 (0.1)</td></tr>
<tr><td>SAS</td><td>B</td><td>30.9 (0.7)</td></tr>
<tr><td></td><td>P</td><td>31.2 (0.2)</td></tr>
<tr><td></td><td>A</td><td>21.6 (0.9)</td></tr>
<tr><td>Y-BOCS</td><td>B</td><td>28.0 (0.6)</td></tr>
<tr><td></td><td>P</td><td>28.0 (0.1)</td></tr>
<tr><td></td><td>A</td><td>17.3 (0.7)</td></tr>
<tr><td>UPDRS -IV items 32-33</td><td>B
P</td><td>4.2 (1.5)
4.1 (1.6)</td></tr>
</table>
</td>
<td>tmt allocation yes 6. Individuals administering care were kept blind to tmt allocation yes 7. All groups followed up for an equal length of time yes 8. Groups comparable for treatment completion? yes 9. Groups were comparable with respect to avalilability of outcome data? yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes 12. Valid and reliable method was used to determine the outcome: yes 13. Investigators were kept blind to participants exposure to the intervention: yes 14. Investigators were kept blind to other important confounding and prognostic factors: unclear

serious risk of bias: unclear how patients were randomised and whether any cross-over effect. Data not</td>
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		withdrawn in 2 days (50mg) during period T4 all patients had 24hr access to clinicians to inform about effects of treatment or of withdrawals	(complications of therapy) | A | 2.2 (0.4)	separated for different arms **Other information** present report showed PG culd be supressed in 2 to 3 days by amantadine and that amanadine withdrawal induced, in a few days, resurgence of the disorder.
Full citation Bastiaens,J., Dorfman,B.J., Christos,P.J., Nirenberg,M.J., Prospective cohort study of impulse control disorders in Parkinson's disease, Movement Disorders.28 (3) (pp 327-333), 2013.Date of Publication: March 2013., 327-333, 2013 Ref Id 306844 Country/ies where the study was carried out USA Study type prospective cohort study	Sample size N=164 outpatients with PD and no previous history of ICD Inclusion criteria nondemented outpatients with PD who presented to a tertiary movement disorders clinic between June 2008 and November 2010. Inclusion criteria were ideopathic PD by UKBB criteria, capacity to provide writeen informed consent and ability to complete a series	Details Subjects followed under routine clinical care and followed prospectively until they reached first of the following pre determined end points: new onset of ICD discontinuation of DAA therapy death or loss to follow up June 30, 2011 Only those who received a predefined minimum exposure to DAA after study enrollment (at least 50 L-dopa equivalent daily dose (LEDD) of DAA for 3 months or more consecutive months) were included within the analysis.	Results frequency and characteristics of ICD 164 patients enrolled in study, of whom 46 subsequently treated with minimum dosage and duration of DAA therapy for inclusion in analysis of these 46, 18 (50% female) developed ICD's after mean duration 21.0 months 6 subjects with ICD lost to follow up mean ICD-free survival time was 68 months (95% CI: 34.8 to 101.2) most common ICD compulsive eating (16/18); 6/18 hyersexuality; 5 compulsive shopping/buying, 1 compulsive gambling concomittent punding present in 12/18 no ICD (-) patients reportd punding behaviours time of onset ICD highly variable (range 3 months 10 years, median 23 months) after initiation of DAA therapy and 1 to 19 years after PD onset diagnosis delayed from between 0 - 15 months afer ICD onset (median 4 months)	**Overall Risk of Bias** 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way?yes - consecutive 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? yes - follow up until reach one of pre-defined end points

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Aim of the study To study prospective incidence time course and risk factors of ICD's Study dates received 9th augus 2012, revised Oct, published Jan 2013 Source of funding The study was supported by a centre grant from the PD foundation	of research questionnaires Exclusion criteria Previous history of ICD, atypical clinical features, MMSE score of <25, clinical diagnosis of dementia, life expectancy of <12 months use of dopaminergic receptor blocking agent, or previous PD neurosurgery	at baseline all subjects avaluated by movement diorder neurologist who completed series of assessments including UPDRS, ADL, MMSE, depression inventory, medication and family history assessment for presence of ICD and punding behaviours occurred at baseline visit and each subsequent visit using semistructured interview involving the subject and all available caregivers interview included broad questions to identify symptoms suggestive of an ICD. If a subject endorsed one or more repetitive behaviours then follow-up questions were asked to determine the scope and consequences of these behaviours . Behaviours classified as ICD's if they disrupted normal work, family, or social interaction or casued negative medical or psychiological consequences.	in 4 subjects (22.2%), incidence of ICD elucidated only through 66.7%)of caregiver or other outside observer risk factors/baseline characteristics baseline demographic characteristics similar between both groups ICD+ grop had significantyly higher prevalence of smoking (44.4% vs 14.3%) and also higher caffeine use (100% vs 66.7%) previous alcoholism rare and same across both groups (88.9% vs 64.3%) at baseline ICD group greater prevalence of motor complications (61.1% vs 25.0%) in contrast, no significant differenes in UPDRS quantitative and qualitiative use of dopaminergic medication same across both groups as was antidepressant and benzodiapepine use trand toward greater familyh istory of depression in ICD group (^1.1%vs 32.1%) endpoint characteristics at endppoint major difference between ICD+/- groups was higher peak DAA dosage in ICD+ grop (median 300 vs 165 LEDD) disease duration. DAA treatment duration, cumulative DAA exposure, specific DAA used, concomittant L-dopa, total LEDD and durattion of dopaminergic therapy were comparable between groups Outcomes in ICD + subjects. ICD resolved in: 10/10 subjects discontinued DAA usage 3/5 reduced DAA dosage 0/3 who continued same dosage concomittent punding occured in 12/18 patients with ICD and resolved in: 5/5 who discontinued DAA therapy 2/4 who reduced DAA dose	7. What are results? study found number of predictive factors for ICD's in prospective cohort 8. How precise are results? only raw data and p- vlaues given. OR's calculated where possible. 9. Are results believable? yes 10. Can results be applied to local population? yes , however all subjects were taking DA. May not be appropriate for patients not taking DA 11. Do results fit with other available evidence? yes 12. What are implications for practice? advise patients taking DA of increased risk of ICD **low risk of bias**

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		ICD status determined at time of each visit, and data on medication usage, caffiene consumption and cigarette smoking behaviours also recorded. Interventions NA	0/3 who continued same dose dopamine agonst withdrawal syndrome (DAWS) occurred in: 6 of ICD subjects; 4 who discontinued use; 1 who reduced dose; 1 who was unable to decrease DAA dose because of severity of DAWS symptoms 4/5 subjects with DAWS developed DDS as they self adjusted l-dopa in unsuccessful attempt to alleviate DAWS symptoms	