5-HT3 RECEPTOR ANTAGONISTS FOR DYSKINESIA

The invention relates to a new medical use for compounds which act as antagonists of 5-hydroxytryptamine (5-HT) at 5-HT_3 receptors.

5-HT_3 receptor antagonists may be identified by methods well known in the art, for example by their ability to inhibit 3-(5-methyl-1H-imidazole-4-yl)-1-[1-[^{3}H]-methyl-1H-indol-3-yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G Kilpatrick *et al*, Nature, 1987, 330, 746-748), and/or by their effect on the 5-HT-induced Bezold-Jarisch (B-J) reflex in the cat (following the general method described by A Butler *et al*, Br. J. Pharmacol., 94, 397-412 (1988)).

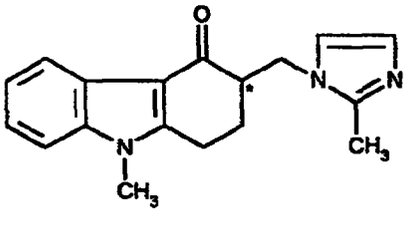
A number of different 5-HT_3 receptor antagonists have been disclosed, for example those mentioned in the following patent applications (and hereinafter referred to as the compounds of Group A):

AU619731	AU626614	AU8658939	AU8660274	AU8716591
AU8767121	EP067770	EP158265	EP158532	EP189002
EP190920	EP191562	EP200444	EP202062	EP210840
EP212802	EP214772	EP219193	EP220011	EP221702
EP230718	EP234872	EP235878	EP237281	EP239321
EP242973	EP254584	EP255297	EP261964	EP266730
EP266899	EP276163	EP287196	EP289170	EP291172
EP294292	EP297651	EP302699	EP306148	EP306323
EP307145	EP307172	EP309423	EP311724	EP313393
EP315316	EP315390	EP317088	EP322016	EP323077
EP327307	EP327335	EP328200	EP329932	EP330788
EP330824	EP336759	EP337547	EP338650	EP339669
EP339950	EP339959	EP344015	EP345956	EP350130
EP351385	EP353983	EP356098	EP357417	EP358903
EP361317	EP361629	EP375045	EP376624	EP377238

EP378111	EP381422	EP385722	EP387431	EP392663
EP393766	EP403261	EP403882	EP405784	EP407137
EP410509	EP419397	EP420086	EP429984	EP430190
EP436245	EP454121	EP456519	EP457243	EP458636
EP469449	EP482939	EP483836	EP485962	EP490263
EP491664	EP498466	EP554794	GB2125398	GB2145416
GB2152049	GB2153821	GB2169292	GB2192885	GB2208385
GB2208862	GB2213816	GB2216516	GB2225574	GB2229182
GB2236528	GB2236751	GB2247886	US4290227	US4486441
US4657911	US4789673	US4816453	US4822881	US4826838
US4857517	US4859683	US4914207	US4920219	US4921982
US4924010	US4935511	US4963689	US4992461	US4997956
US5030646	US5063230	US5116984	US5137893	WO8403281
WO8801866	WO8909217	WO9006309	WO9101316	WO9104738
WO9107402	WO9112254	WO9116888	WO9117161	WO9205174
WO9206689	WO9209284	WO9212149;		

all incorporated herein by reference. The above applications also describe, in relation to the 5-HT_3 receptor antagonists they disclose, both suitable methods for their preparation and doses for their administration.

In UK Patent No. 2153821B there is disclosed, *inter alia*, 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, now known as ondansetron, which may be represented by the formula (I)



(I)

and pharmaceutically acceptable salts, solvates and pharmaceutically acceptable equivalents thereof.

Particular examples of compounds from within Group A include the compounds of Group B, namely:

endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (itasetron);
endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide (BIMU 1);
endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl indole-3-carboxylate (tropisetron);
endo-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methylimidazole-3-carboxamide (granisetron);
trans-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)one (dolasetron), preferably in the form of its mesilate;
endo-5-chloro-2,3-dihydro-2,2-dimethyl-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-7-benzofuran carboxamide (zatosetron);
4-amino-N-[1-azabicyclo(2.2.2)oct-3-yl]-5-chloro-2-methoxy benzamide (zacopride), more preferably (R) zacopride;
4-[N-(1-azabicyclo[2.2.2]octan-3-(5)-yl)]2-chloro-cis 5a-(s)-9a-(s)-5a,6,7,8,9,9a-hexahydrobenzofurancarboxamide (RG-12915);
4-amino-5-chloro-N-[2-pyrrolidylamethyl]-2,3-dihydrobenzo[b]furan-7-carboxamide (ADR-851);
4-amino-N-[1-azabicyclo[2.2.1]oct-3-yl]-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide (ADR-882);
(R)-5-[(1-methyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole (YM060);
(±)-N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide (azasetron);
endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethyl indole-1-carboxamide (BRL 46470); and
2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (alosetron), preferably as its hydrochloride;
6-fluoro-2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (lurosetron), in particular in the form of its mesilate dihydrate;

4H-pyrido(3,2,1-jk)carbazol-11(8H)-one, 5,6,9,10-tetrahydro-10-((2-methyl-1H-imidazol-1-yl)methyl)-, (R)- (cilansetron);
benzamide, 4-amino-5-chloro-N-(8-methyl-8-azabicyclo(3.2.1) oct-3-yl)-2-((1-methyl-2-butynyl)oxy)-, monohydrochloride, (3(S)-endo) (E-3620);
pyrido(1,2-a)indol-6(7H)-one, 8,9-dihydro-10-methyl-7-((5- methyl-1H-imidazol-4-yl)methyl)-, monohydrochloride, (+)- (FK-1052);
benzamide, 4-amino-N-1-azabicyclo(2.2.2)oct-3-yl-5-chloro-2-(cyclopropylmethoxy)-, (+/-)- (pancopride); and
7-methoxy-1H-indole-3-carboxylic acid, 8-methyl-8-azabicyclo(3.2.1)oct-3-yl ester.

It will be appreciated by the skilled person that, as a consequence of the use of different chemical naming conventions (e.g. IUPAC, CA), a compound in Group B may be referred to by a different chemical name within the corresponding patent application in Group A.

Other examples of suitable 5-HT_3 receptor antagonists for use according to the invention include the compounds of Group C, namely:

1H-Indole, 2,3-dihydro-1-((4,5,6,7-tetrahydro-1H-benzimidazol-5-yl)carbonyl)-, monohydrochloride, (R)- (YM-114);
1H-Benzimidazole, 1-(phenylmethyl)-2-(1-piperazinyl)- (lerisetron);
endo-3,9-dimethyl-3,9-diazabicyclo(3.3.1)non-7-yl-1H-indazole-3-carboxamide dihydrochloride (N-3389);
RS-25259;
endo-8-methyl-8-azabicyclo(3.2.1)oct-3-yl 1-isobutyl-2-oxo-1,2-dihydro-4-quinuclidinecarboxylate (KF-18259);
2-methoxy-4-amino-5-chloro-N-(hexahydro-1H,2,5beta-methano- 3alpha,6alpha-cyclopenta(c)-pyrrol-4alpha-4-(R)-yl) benzamide hydrochloride (SC-52491);
(3aS)-(2-((S)-1-azabicyclo(2.2.2)oct-3-yl)-2,3,3a,4,5,6- hexahydro-1H-benz(de)isoquinolin-1-one hydrochloride;
endo-1-Cyclohexyl-N-(8-methyl-8-azabicyclo(3.2.1)octan-3-yl)-4-oxo-1,4-dihydrquinoline-3-carboxamide (mirisetron);
6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-piperazinyl) benzimidazole dimaleate (KB-6933);
(+)-endo-4-(propionyloxy)-6-(4-fluorophenyl)-1-azabicyclo(3.3.1)non-6-ene hydrochloride (GYKI-46903); and

3-(2-(4'-piperonylpiperazinyl)indol)carboxyaldehyde (VA-21B7).

5-HT_3 receptor antagonists are known to be useful in the treatment of a variety of conditions involving 5-HT_3 receptor-mediated mechanisms, including in particular emesis.

Abnormal involuntary movements or dyskinesias include, *inter alia*, tremor, chorea, myoclonus and tics. In addition to these categories of dyskinesia, there is a particular set of involuntary movements known as tardive dyskinesia or drug-induced tardive dyskinesia.

Tremor is an abnormal involuntary trembling or quivering. It may be characterised as a rhythmic sinusoidal movement of a body part caused by regular rhythmic muscle contractions.

Chorea consists of a continuous flow of irregular, jerky, and explosive movements, that flit from one portion of the body to another in random sequence. Each muscle contraction is brief, often appearing as a fragment of what might have been a normal movement, and quite unpredictable in timing or site.

Myoclonus consists of rapid shock-like muscle jerks, often repetitive and sometimes rhythmic.

Tics are similar to myoclonic jerks in appearance, but are repetitive, stereotyped movements that can be mimicked voluntarily and can be held in check by an effort of will at the expense of mounting inner tension.

Tardive dyskinesia is typically marked by involuntary repetitive movements of the facial, buccal, oral and cervical musculature,

Current medical therapies for dyskinesia, in particular where dyskinesia is the solitary feature of the illness (e.g. benign essential (familial) tremor and benign essential (myoclonus)), include alcohol; benzodiazepines, such as diazepam, lorazepam and clonazepam; and β-adrenergic receptor antagonists, such as propranolol. Other dyskinesias are often a facet of another neurological disease and treatment of the dyskinesia follows that appropriate for the relevant neurological disease. Thus, for example, the treatment of tremor caused by

Parkinson's disease may be by dopaminergic agents such as levodapa and antimuscarinic agents such as benzhexol.

Nevertheless, many patients gain slight or even no relief from such agents. Furthermore, the side effect profiles of such drugs severely limit their clinical use. Thus, there is a real need to develop new medicines for the treatment of dyskinesia.

Surprisingly, it has now been found that 5-HT_3 receptor antagonists are also of use in the treatment of dyskinesia.

According to one aspect the invention therefore provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of dyskinesia.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt or solvate of a 5-HT_3 receptor antagonist or any other compound, which upon administration to the recipient is capable of providing (directly or indirectly) a 5-HT_3 receptor antagonist or an active metabolite or residue thereof.

In one preferred aspect the invention provides a compound of Group A or a pharmaceutically acceptable derivative thereof, more preferably a compound of Group B or a pharmaceutically acceptable derivative thereof, for use in the treatment of dyskinesia.

In a further preferred aspect the invention therefore provides ondansetron or a pharmaceutically acceptable derivative thereof for use in the treatment of dyskinesia.

Suitable pharmaceutically acceptable salts of ondansetron include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, salicylates, succinates, lactates, glutarates, glutaconates, acetates, tricarballylates, citrates, fumarates and maleates), and solvates (for example hydrates) thereof.

In a preferred embodiment of the present invention ondansetron is employed in the form of its hydrochloride, more preferably its hydrochloride dihydrate.

In another preferred embodiment of the present invention ondansetron is employed in the form of its free base.

It will be appreciated by those skilled in the art that ondansetron contains one chiral centre (shown by * in the formula (I)) and that ondansetron therefore exists in the form of optical isomers (i.e. enantiomers). The invention includes all isomers of ondansetron and its pharmaceutically acceptable derivatives, including all tautomeric and optical forms, and mixtures thereof, including racemic mixtures.

Each type of dyskinesia may be caused by a variety of diseases. It may be accompanied by other neurological deficits or the abnormal involuntary movements may occur in isolation and constitute the illness. 5-HT_3 receptor antagonists are in particular useful in the treatment of tremor, chorea, myoclonus, tics, and tardive dyskinesia.

Tremor includes rest tremor, postural tremor and intention tremor. Rest tremor may be caused by, for example, Parkinson's disease, post-encephalitic Parkinsonism, drug-induced Parkinsonism and other extrapyramidal diseases. Postural tremor may be caused by, for example, physiological tremor; exaggerated physiological tremor attributable to, for example, thyrotoxicosis, anxiety states, alcohol, drugs (such as, sympathomimetics, anti-depressants and lithium) and heavy metal poisoning (such as mercury); hyperthyroidism, structural brain disease attributable to, for example, severe cerebellar lesions, Wilson's disease and neurosyphilis; and benign essential (familial) tremor. Intention tremor may be caused by, for example, brain stem or cerebellar disease attributable to, for example, multiple sclerosis (MS), spinocerebellar degenerations, vascular disease and tumour.

Chorea includes Sydenham's chorea, Huntington's disease, benign hereditary chorea, symptomatic chorea, drug-induced chorea and hemiballism (hemichorea).

Myoclonus includes generalised myoclonus, such as progressive myoclonic encephalopathies, static myoclonic encephalopathies, myoclonic epilepsies, benign essential (familial) myoclonus and focal myoclonus (segmental).

Tics include simple tics, complex multiple tics (e.g. Gilles de la Tourette syndrome) and symptomatic tics.

Tardive dyskinesia may develop following the treatment of, for example, psychotic disorders (such as schizophrenia and mania) with neuroleptics, such as phenothiazines; and cognitive disorders such as dementia (e.g. Parkinson's disease), with dopaminergic agents, such as levodopa. Tardive dyskinesia may persist after withdrawal of the treatment.

In a preferred aspect the invention provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of tremor.

In another preferred aspect the invention provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of benign essential (familial) tremor.

Benign essential (familial) tremor may present at any age and is often inherited as an autosomal dominant trait. It is characterised by postural tremor of the arms and head, although the jaw, tongue, legs and trunk may also be affected.

In a further preferred aspect the invention provides a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of intention tremor.

In another aspect, the invention provides a method of treatment of a mammal, including man, suffering from dyskinesia which comprises administering an effective amount of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof.

In another aspect, the invention provides the use of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of dyskinesia.

Within the above aspects and preferred aspects of the invention, the use of a 5-HT_3 receptor antagonist of Group A, more preferably a 5-HT_3 receptor antagonist of Group B, most preferably ondansetron, is especially preferred.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

Conveniently, a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients. Thus a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may, for example, be formulated for oral, sub-lingual, buccal, parenteral, rectal or intranasal administration, or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose), or in a form suitable for topical administration.

For oral administration the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrates (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

A 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, optionally with an added preservative.

The compositions for parenteral administration may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the compositions may be in dry form such as a powder, crystalline or freeze-dried solid for constitution with a suitable vehicle, e.g. sterile pyrogen-free water or isotonic saline before use. They may be presented, for example, in sterile ampoules or vials.

A 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may also be formulated in rectal compositions such as suppositories or retention enemas.

Tablets for sub-lingual administration may be formulated in a conventional manner.

For intranasal administration, or administration by inhalation or insufflation, a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may be formulated in a conventional manner.

For topical administration the pharmaceutical compositions may be liquids, for example solutions, suspensions or emulsions presented in the form of creams or gels.

In addition to the formulations described previously, a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Pharmaceutical formulations of ondansetron or a pharmaceutically acceptable derivative thereof may be prepared, for example, according to UK Patent No. GB 2153821B, European Patent Application Publication No. 276559 or International Patent Application Publication Nos. WO94/27599, WO96/15785 or WO96/15786.

It will be appreciated that the precise therapeutic dose of a 5-HT_3 receptor antagonist, expressed in the form of its free base, will depend on the age and condition of the patient and the nature of the dyskinesia to be treated, and will be at the ultimate discretion of the attendant physician.

However, in general, effective doses for the treatment of dyskinesia, in particular, tremor will lie in the range of 0.001 to 500mg, such as 0.01 to 100mg, preferably 0.05 to 50mg, for example 0.5 to 25mg per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

In a preferred embodiment, effective doses of ondansetron for the treatment of tremor will lie in the range of 0.05 to 100mg, such as 0.1 to 50mg, preferably 0.5 to 25mg, for example 2, 4, 8 or 16mg of ondansetron per unit dose, which could be administered in single or divided doses, for example, 1 to 4 times per day.

The use of ondansetron in the treatment of dyskinesia is supported by the following clinical data.

A placebo-controlled, double blind, crossover study of intravenous ondansetron in twenty patients with cerebellar tremor caused by MS, cerebellar degeneration or drug toxicity was conducted.

Most had tremor based upon cerebellar involvement from MS; three had familial degenerative disorders involving the cerebellum and one had acquired lithium toxicity. The clinical information and prior treatment of the patients is outlined below in Table 1.

Patients were randomly assigned to receive intravenous ondansetron (8mg or a placebo, consisting of normal saline). The drug was given by intravenous bolus injection. Patients were given the alternate agent at a later interval.

The principal outcome measure was the change in manual co-ordination tasks as assessed by spiral copying, word copying or line drawing and the time to complete a nine-hole peg test. Only 12 patients had sufficient co-ordination to complete the nine-hole peg test.

The clinical outcome was measured at baseline and one hour following the infusion.

Figures 1 (a), (b) and (c) represent an attempt to copy a spiral by the first mentioned patient in Table 1. Figure 1(a) represents an attempt prior to treatment with ondansetron; figure 1 (b) an attempt after receiving placebo; and figure 1 (c) an attempt after receiving ondansetron.

Results

The patient profile and clinical outcomes are shown in Table 1.

Table 1

Disease	Tremor Type & Clinical Findings	Prior Treatment	Placebo response	Subjective drug response	Spiral Writing placebo	Spiral Writing drug	9 hole peg-placebo (secs)	9 hole peg-drug (secs)
Cd[1]	Intention, postural	Clonazepam	None	++	0	+++	101	85
Cd	Intention		None	+++	0	++	62	45
Cd[2]	Intention	Clonazepam	NT	+ (dysarthria)	NT	NT	NT	NT
Lithium	Intention/ dysarthria	Clonazepam Valproste	None	0	0	0	47	55
MS	Intention	Clonazepam	None	+++	0	+++	84	70
MS	Intention	Clonazepam	None	+++	0	+++	NT	NT
MS	Intention	None	None	++	0	+	37	29
MS	Intention	None	None	+	0	+	NT	NT
MS	Intention	None	None	++	0	++	NT	NT
MS	Intention	None	None	++	0	+	140	110
MS	Intention	None	None	++	0	+++	NT	NT
MS	Intention	None	None	0	+	+	78	63
MS	Intention	None	None	+	0	++	NT	NT
MS	Intention	None	None	0	0	0	157	155
MS	Intention	None	None	0	0	+	65	55
MS	Intention	None	None	0	0	0	65	48
MS	Intention	None	None	0	0	0	NT	NT
MS	Intention/ dysarthria	None	None	0	0	+	160	180
MS	Intention/ dysarthria	None	None	+	0	++	NT	NT
MS	Intention	None	NT	0	0	0	54	57
Ratio			0/18	12/20	1/19	13/19		
Mean							87±12	79±13

Key

Improvement was measured on a singe ordinal scale:
0 = none, + = a little, ++ = moderate, +++ = a lot of improvement,

[1]The spiral writing of this patient is shown in Figure 1(a), 1(b) and 1(c);
[2]The development of dystonia in this patient dissipated enthusiasm to continue in the study;
Cd = Cerebellar degeneration.

A favourable clinical response was identified by a panel of three blind observers in 13 of the 20 patients; the same observers identified a response in one placebo-treated patient. The difference was significant in the entire study group (p=0.009; Fisher exact ratio), and the MS subgroup of 16 patients, 13 of whom has a response (p=0.001).

The completion of a timed task, the nine hole peg test, was improved in patients who received ondansetron. The mean time for the completion of this task was 79 ± 13 (standard error) seconds in patients treated with ondansetron and 87 ± 12 seconds in placebo-treated patients, (p=0.04; Mann Whitney; one tailed test for paired data). One further patient with cerebellar degeneration too disabled to complete these tasks (Cd^2, Table 1), was noticed to have improved speech after treatment with ondansetron.

Patient identification of treatment assignment was correct in 12/20 instances and this was based upon efficacy. None believed placebo to be better (p=0.014; Fisher exact ratio).

The recruitment of patients was biased to select the most severely challenged patients. Most patients required walking assistance. After the study was completed, it was apparent that the best responses were seen in the less disabled patients. Among the patients with MS, a better response was seen in patients with more recent onset ataxia.

Ondansetron was well tolerated and the effect could be sustained in the long term. Withdrawal of the medication resulted in the tremor returning to pre-study levels. Nothing worked well for the tremor in these patients prior to the use of ondansetron.

The effect of intravenous ondansetron could be reproduced with oral ondansetron (8-16mg).

Claims

1. Use of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of dyskinesia.

2. Use according to claim 1 wherein the dyskinesia is tremor.

3. Use according to claim 2 wherein the tremor is benign essential (familial) tremor.

4. Use according to claim 2 wherein the tremor is intention tremor.

5. Use according to any one of claims 1-4 wherein the 5-HT_3 receptor antagonist is ondansetron or a pharmaceutically acceptable derivative.

6. Use according to claim 5 wherein ondansetron is in the form of its hydrochloride or hydrochloride dihydrate.

7. Use according to claim 5 wherein ondansetron is in the form of its free base.

8. Use according to any one of claims 1-4 wherein the 5-HT_3 receptor antagonist is selected from granisetron, tropisetron, azasetron, dolasetron, alosetron or (R) zacopride.

9. A method of treatment of a mammal, including man, suffering from dyskinesia which comprises administering an effective amount of a 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof.

10. A 5-HT_3 receptor antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of dyskinesia.