Title: USE OF METFORMIN TO COUNTERACT WEIGHT GAIN ASSOCIATED WITH ARIPIPRAZOLE OR ZIPRASIDONE TREATMENT

Abstract: A method for minimizing the weight gain side effect associated with ABILIFY® (aripiprazole) or GEODON® (ziprasidone) treatment is disclosed. In this method, metformin, a biguanide compound, is concurrently administered to a patient taking the ABILIFY® (aripiprazole) or GEODON® (ziprasidone) therapy. A pharmaceutical composition containing the combination of ABILIFY® (aripiprazole) or GEODON® (ziprasidone), together with metformin, is also disclosed.
USE OF METFORMIN TO COUNTERACT WEIGHT GAIN ASSOCIATED
WITH ARIPIPRAZOLE OR ZIPRASIDONE TREATMENT

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CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application is related to and claims priority from U.S. Provisional Patent Application No. 60/675,534, Cottingham, filed April 28, 2005, incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention relates to improvements in the treatment of patients for schizophrenia, bipolar disorder, psychosis and other psychiatric illnesses.

BACKGROUND OF THE INVENTION

[0003] ABILIFY® (aripiprazole) is a psychotropic drug that is available in tablet form for oral administration. It functions as a dopamine partial agonist and, as a result of this unique mechanism, is thought to be different from the other atypical antipsychotic drugs.

[0004] GEODON® (ziprasidone) is also a psychotropic drug available as capsules for oral administration. It is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents.

[0005] In general, the known antipsychotic agents cause weight gain in the patients taking them. This can be a difficult side effect to deal with, since it can easily result in non-compliance by the patient (i.e., the patient stops taking the drug or takes it at reduced frequency) leading to major problems. Although ABILIFY® and GEODON® were thought to result in reduced weight gain seen, there is still
significant weight gain, at least in some patients. For example, Jaworowski, S. et al., Ziprasidone and Weight Gain, Clin. Neuropharmacol. 2004 March-Apr 27(2):99-100, reported significant weight gain in a 12-year-old male treated with GEODON®.

Clearly, from both a compliance and a patient self-esteem point-of-view, it would be very helpful to eliminate or minimize the weight gain caused by ABILIFY® and GEODON®.

The use of metformin to counteract weight gain in patients caused by the psychotropic actives DEPAKOTE® (valproate), RESPERDAL®, LITHOBID®, ZYPREXA® and SEROQUEL® is taught in U.S. Patent 6,194,466, Cottingham and Morrison, issued February 27, 2001.

SUMMARY OF THE INVENTION

The present invention relates to a method for minimizing weight gain in a patient taking a psychotropic active selected from the group consisting of ABILIFY® (aripiprazole) and GEODON® (ziprasidone), comprising the administration to said patient of a safe and effective amount of metformin or a similar compound.

The present invention also encompasses a combination drug composition which comprises a safe and effective amount of a psychotropic active select from the group consisting of ABILIFY® (aripiprazole) and GEODON® (ziprasidone), together with a safe and effective amount of metformin or a similar compound.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for minimizing weight gain in a patient taking the antipsychotic medications ABILIFY® and GEODON®.

ABILIFY® (aripiprazole) is an antipsychotic drug that is available as tablets for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. Its empirical formula is C_{23}H_{27}Cl_{2}N_{3}O_{2} and its molecular weight is 448.38. The structural formula of the compound is
Aripiprazole is chemically different from other atypical antipsychotic agents and is also believed to have unique pharmacological actions that are different from other atypical antipsychotic drugs, including ZYPREXA®, SEROQUEL® and RISPERDAL®. Aripiprazole acts as a weak stimulator (so-called “partial” agonist) at dopamine D₂ receptors, with the potential for exerting either antagonistic (inhibitory) or agonistic (stimulating) effects, depending on the sensitivity of the receptors and the availability of dopamine, its natural agonist in the brain. Aripiprazole also has similar activity at serotonin-5-HT₁A receptors, as well as acting as an agonist at serotonin-5-HT₂A receptors, and having a number of other lesser actions.

GEODON® is available as GEODON® capsules (ziprasidone hydrochloride) for oral administration. Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has an empirical formula of C₂₁H₂₁ClN₄OS (free base) and a molecular weight of 412. Its chemical name is 5-[(2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-6-chloro-1,3-dihydro-2H-indol-2-one; and the following structural formula

Other pharmaceutically acceptable salts of both of these actives may also be used herein.
Although they are both effective antipsychotic agents, both ABILIFY® and GEODON® cause some degree of weight gain in many patients. It is that effect which the present invention addresses.

Metformin hydrochloride is a biguanide compound that is generally prepared as an oral anti-hyperglycemic drug used in the management of non-insulin-dependent diabetes mellitus. It is typically prepared in the form of tablets and is commercially available as GLUCOPHAGE® from the Bristol-Myers Squibb Company. It is also available as a liquid for oral administration. Metformin hydrochloride (N,N-dimethylimidocarbonimidic diamide hydrochloride) has the structural formula shown below:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} & \quad \text{C} & \quad \text{NH} & \quad \text{C} & \quad \text{NH}_2 & \cdot \text{HCl} \\
\text{H}_3\text{C} & \quad \text{NH} & \quad \text{N} & \quad \text{NH}
\end{align*}
\]

In addition to metformin hydrochloride, other pharmaceutically acceptable salts of metformin may be used. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C_{4}H_{11}N_{5}·HCl, and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether or chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. GLUCOPHAGE® tablets contain 500 mg or 850 mg of metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate and hydroxypropyl methylcellulose coating.

The metformin dosage forms used in the present invention optionally may be formulated for controlled release, sustained release, delayed release, or response release (i.e., the tablet is ingested and the active is released in response to the
occurrence of a precondition in the patient, such as the intake of food by the patient, or changes in pH, sugar levels or osmolarity in the patient).

In practicing the method of treatment of the present invention, metformin (or another pharmaceutically acceptable salt of N,N-dimethylimidocarbonimidic diamide) is administered to a patient on ABILIFY® or GEODON® therapy. The psychotropic actives will be administered using their conventional routes of administration and their conventional dosage levels. Metformin may be administered to the patient in any way known in the art, although oral administration will generally be most convenient. Metformin is administered in an amount that is safe and effective for minimizing the weight gain associated with ABILIFY®/GEODON® therapy, preferably at a level of from about 1500 to about 2500 mg per day. It is typically administered with meals at a dosage of 500 mg tid.

The present invention also encompasses a combination drug that includes the active found in ABILIFY® or GEODON® (or other pharmaceutically acceptable salts), together with metformin or other biguanide compounds (including other pharmaceutically acceptable salts of N,N-dimethylimidocarbonimidic diamide). This combination of drugs is typically formulated as a tablet or capsule for oral administration, although other routes of administration, such as intravenous injection can also be used. A tablet or capsule for oral administration of the present invention would typically include from about 2.5 mg to about 30 mg of ABILIFY® or from about 20 mg to about 80 mg GEODON®, and from about 250 mg to about 850 mg of metformin. Conventional formulational aides, such as fillers, coatings, preservatives, disintegration aides, colorings and flavorings, can also be included at their conventional art-established levels.
By “pharmacologically acceptable,” as used herein, is meant that the drug-active compounds and other ingredients used in the present methods and compositions, are suitable for use in contact with the tissues of humans without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

**CASE STUDY**

**Presentation & Diagnosis**

A 10-year-old female presented with behavioral problems. The patient had an extensive history of behavioral problems, including issues with authority figures, problems with anger modulation and management, and instances of explicit sexual behavior.

The patient was adopted, and she lived with her adoptive parents and her non-biological sister. Academically, she was reported to be doing well, she had positive peer relations, and was involved in cheerleading and sporting activities such as basketball and softball.

On presentation, the patient's parents were primarily concerned with her mood labiality. They observed that she could go from "sweet" to "angry" on a daily basis. She had episodes of nocturnal restlessness; she exhibited difficulty concentrating, and was both disorganized and inattentive. Her energy level was described as appropriate, however she had a history of aggressive and destructive behavior. For example, she peeled wallpaper off the walls, broke blinds, and damaged spindles on the stairs. She had physically attacked her mother, leaving scratches and bruises. She was reported to be oppositional and defiant, calling her mother names and refusing to abide by the rules and regulations of the household. She had also been caught stealing money within the home.
During the psychiatrist's interview, the patient reported feeling angry with her parents about scheduling an appointment, and was unhappy in general. While initially uncooperative, she participated more as the evaluation progressed. She demonstrated a lack of insight regarding her behaviors and overall poor judgment. However, she denied suicidal or homicidal ideation, or any symptoms of psychosis.

**Diagnosis**

The patient's presentation was strongly suggestive of Bipolar Affective Disorder, Not Otherwise Specified (BPAD NOS). The time of onset for childhood BPAD is frequently during the later years of the latency period, and typically includes rapid cycling, with disturbances in sleep, behavioral issues including aggression, grandiosity, and hyper-sexuality. At the time of evaluation, it was difficult to know if the patient also had co-occurring ADHD, combined subtype and Oppositional Defiant Disorder. Bipolar Affective Disorder, NOS appeared to be the more parsimonious diagnosis.

**Treatment and Outcome**

Given the complexity of making a diagnosis of BPAD in children and adolescents, the parents were encouraged to read about BPAD and treatment with medication. Additionally they were asked to keep a mood chart. On their return visit, the parents agreed that the patient's symptoms were most consistent with BPAD, and believed that she primarily had manic symptoms. Various medications were discussed to achieve mood stabilization in the patient, including lithium, divalproex, various anticonvulsants, and the atypical antipsychotics. After full discussion of the risks, side effects and advantages of each medication, including concerns about frequent laboratory monitoring, weight gain and end organ effects, she was started on
aripiprazole (5 mg, once daily). Parents were also directed to seek psychotherapy for the patient and the family, to assist with the management of her BPAD.

On a return visit 2 weeks later, the patient was reportedly much more settled, with fewer outbursts, and no behavioral concerns. The patient continued to do well on aripiprazole, but she gained weight: having started the treatment at 78 lbs, increasing to 110 lbs in approximately six months.

The patient was started on metformin (titrated to 500 mg, twice daily) together with the aripiprazole, to remediate the weight gain. She tolerated the metformin without side effects, and she exhibited a subsequent decrease in her Body Mass Index (BMI), from 24.9 to 22.6, over a 3-month period, a decrease of seven pounds. The patient continued on this regimen and had no additional concerns about her weight.

References

Management options for bipolar disorder in children and adolescents.

Journal: Paediatr Drugs (Author: Danielyan, A; Kowatch, RA; Year: 2005; Vol: 7(5); Pages: 277 - 297)

Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States.

Journal: Arch Pediatr Adolesc Med (Author: Curtis, LH; Masselink, LE; Ostbye, T; Year: 2005; Vol: 159(4); Pages: 362 - 366)

Weight change with atypical antipsychotics in the treatment of schizophrenia.

Journal: J Psychopharmacol (Author: Haddad, P; Year: 2005; Vol: 19(6); Pages: 16 - 27)
Metformin for weight loss in pediatric patients taking psychotropic drugs.

**Journal:** Am J Psychiatry (*Author:* Morrison, JA; Cottingham, EM; Barton, BA;  
**Year:** 2002;  
**Vol:** 159(4);  
**Pages:** 655 - 657)

Options for pharmacological management of obesity in patients treated with atypical antipsychotics.

**Journal:** Int Clin Psychopharmacol (*Author:* Werneke, U; Taylor, D; Sanders, TA;  
**Year:** 2002;  
**Vol:** 17(4);  
**Pages:** 145 - 160)

Clinical experience with Topiramate to counteract neuroleptic induced weight gain in 10 individuals with autistic spectrum disorders.

**Journal:** Brain Dev (*Author:* Canitano, R;  
**Year:** 2005;  
**Vol:** 27(3);  
**Pages:** 228 - 232)

A Double-Blind, Placebo-Controlled Trial of Sibutramine for Olanzapine-Associated Weight Gain.

**Journal:** Am J Psychiatry (*Author:* Henderson, DC; Copeland, PM; Daley, TB;  
**Year:** 2005;  
**Vol:** 162(5);  
**Pages:** 954 - 962)

Double blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine.

**Journal:** Amer J of Psychiatry (*Author:* Graham, KA; Gu, H; Lieberman, JA;  
**Year:** 2005;  
**Vol:** 162;  
**Pages:** 1744 - 1746)

What is claimed is:
CLAIMS

1. A method for minimizing weight gain in a patient taking a psychotropic active selected from the group consisting of aripiprazole and ziprasidone, comprising the administration to said patient of a safe and effective amount of a weight control active compound comprising a pharmaceutically-acceptable salt of N,N-dimethylimidocarbonimidic diamide.

2. The method according to claim 1 wherein the weight control active is the hydrochloride salt.

3. The method according to claim 2 wherein the psychotropic active is aripiprazole.

4. The method according to claim 3 wherein the weight control active is administered orally.

5. The method according to claim 4 wherein the weight control active is administered in an amount of from about 1500 mg to about 2500 mg per day.

6. A pharmaceutical composition comprising a safe and effective amount of a psychotropic active selected from the group consisting of aripiprazole and ziprasidone, together with a weight control active comprising a pharmaceutically-acceptable salt of N,N-dimethylimidocarbonimidic diamide in an amount safe and effective for minimizing weight gain caused by said psychotropic active in the patient taking said psychotropic active.

7. The composition according to claim 6 wherein the weight control active is the hydrochloride salt.

8. The composition according to claim 7 wherein the psychotropic active is aripiprazole.

9. The composition according to claim 8 which is formulated for oral administration.

10. The composition according to claim 9 which contains from about 2.5 mg to about 30 mg aripiprazole, and from about 250 mg to about 850 mg of the weight control active.
11. The composition according to Claim 6 wherein the psychotropic active is ziprasidone present at from about 20 mg to about 80 mg, and from about 250 mg to about 850 mg of the weight control active.

12. Use of a pharmaceutically-acceptable salt of N,N-dimethylimidocarbonimidic diamide for manufacture of a composition for use in minimizing weight gain in a patient taking a psychotropic active selected from the group consisting of aripiprazole and ziprasidone.

13. The use according to claim 12 wherein the pharmaceutically acceptable salt is the hydrochloride salt.
INTERNATIONAL SEARCH REPORT

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 00/21522 A (CHILDREN'S HOSPITAL RESEARCH FOUNDATION; MORRISON, JOHN, AINSLIE; COTT) 20 April 2000 (2000-04-20) abstract page 4, line 1 - page 5, line 10 claims 1-15</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed
  *R* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  *&* document member of the same patent family

Date of the actual completion of the international search: 25 August 2006
Date of mailing of the international search report: 06/09/2006

Name and mailing address of the ISA:
European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HI Wassenaar
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Authorized officer: Langer, O

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**INTERNATIONAL SEARCH REPORT**

**Box II** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 1–5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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<td>DE 69910600 T2</td>
<td>24-06-2004</td>
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<td>EP 1121110 A1</td>
<td>08-08-2001</td>
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<td>27-02-2001</td>
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