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Bodyweight Gain with Atypical Antipsychotics

A Comparative Review

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Abstract

The atypical antipsychotics have been shown to have superior efficacy com-

pared with typical antipsychotics such as haloperidol, particularly in the treatment of negative symptoms of schizophrenia. Furthermore, they induce less extrapyramidal effects. However, following clinical use, marked bodyweight gain has been frequently observed with some of the atypical antipsychotic drugs.

In order to examine and compare the frequency, amount and conditions of bodyweight gain during treatment with atypical antipsychotics, studies concerning bodyweight gain with these agents were identified through a MEDLINE search from 1966 to March 2000.

Although comparison is limited by the different designs and recruitment procedures of the reviewed studies, the available data support the notion that the frequency as well as the amount of bodyweight gain is high in patients treated with olanzapine (average bodyweight gain 2.3 kg/month), clozapine (1.7 kg/month), quetiapine (1.8 kg/month), and possibly also zotepine (2.3 kg/month). Moderate changes in bodyweight have been observed in the treatment with risperidone (average bodyweight gain 1.0 kg/month). Ziprasidone seems to induce only slight bodyweight changes (0.8 kg/month). Bodyweight gain most frequently occurs in the first 12 weeks of treatment. Patients who were underweight at the beginning of treatment are at highest risk of gaining bodyweight.

The underlying pathomechanism still remains largely unclear. The relative receptor affinities of the atypical antipsychotics for histamine H_1 receptors as well as the ratio of their affinity for serotonin 5-HT_2 and dopamine D_2 receptors appear to be the most robust correlate of bodyweight gain. Furthermore, the induction of leptin secretion may have an important impact on bodyweight gain in patients treated with atypical antipsychotics.

Although many questions concerning the pathogenesis of bodyweight gain remain unresolved, this adverse effect has to be taken into consideration when prescribing the atypical antipsychotics, particularly in view its affect on compliance during long term treatment and the long term effects of obesity on mortality and morbidity.

1. Atypical and Typical Antipsychotics

The antipsychotic drug clozapine, which was developed in the late 1950s and introduced into clinical use in 1971, shows some pharmacological properties that are different from those of the typical antipsychotics such as the phenothiazines (e.g. chlorpromazine) and butyrophenones (e.g. haloperidol). The most clinically relevant difference between clozapine and the typical antipsychotics is its comparative lack of extrapyramidal effects (EPS) and its good therapeutic efficacy in treating the negative symptoms of schizophrenia. Because of this atypical clinical profile clozapine was often called an 'atypical' antipsychotic drug. Up until recently, there was no concise and well accepted definition of an atypical antipsychotic drug.[1,2] In addition, the pharmacological profile of clozapine differs in many aspects from that of the typical antipsychotics (see table 1).[3,4] Clozapine has a relatively low affinity for the dopamine D_2 receptor, and a high affinity for the serotonin 5-HT_2 receptor with antagonistic effects. Moreover, clozapine has strong antihistaminergic and anticholinergic effects. However, the different ratio of the affinity for 5-HT_2 and D_2 receptors is judged to be the most pronounced difference between atypical and typical antipsychotic drugs. Most of the new atypical antipsychotics have been designed to show a similar pharmacological profile to clozapine without its severe haematological adverse effects (agranulocytosis). They can be classified into different chemically defined groups: thienobenzodiazepines (e.g. clozapine and olanzapine); dibenzothiepines (e.g. quetiapine and

Table I. Pharmacological profile of different atypical antipsychotics in relation to the calculated average monthly bodyweight gain[3,4,5]a

Drug	M_1	D_1	D_2	5-HT_{2a}	5-HT_{2c}	H_1	5-HT_2/D_2	Average monthly bodyweight gain (kg)
Olanzapine	++++++	+++++	++++++	++++++	++++++	+++++	0.90	2.28
Zotepine	+++++	+++++	++++++	++++++	++++++	+++++	0.18	2.28[b]
Quetiapine	++++	++++	++++	+++++	++++	+++	1.18	1.76[c]
Clozapine	++++++	+++++	+++++	+++++	+++++	+++++	0.11	1.72
Risperidone	++	+++++	++++++	++++++	+++++	++++	0.88	0.96
Ziprasidone	+	++++	++++++	++++++	++++++	++++	0.12	0.80[b]

a Receptor affinity (K_i values in mol/L): + = 10^{-1}; ++ = 10^{-2}; +++ = 10^{-3}; ++++ = 10^{-4}; +++++ = 10^{-5}; ++++++ = $\leq 10^{-6}$).

b Data from only 2 studies.

c Data only from studies with treatment duration ≤ 8 weeks.

5-HT = serotonin (5-hydroxytryptamine) receptors; **D** = dopamine receptors; **H** = histamine receptors; **M** = muscarinic acetylcholine receptors.

zotepine); benzisoxazoles (e.g. risperidone); and others (e.g. ziprasidone).

2. Problem of Bodyweight Gain

Increasingly, bodyweight gain is becoming recognised as a problematic adverse effect of atypical antipsychotics. However, an increase in bodyweight is a known adverse effect of many psychotropic drugs, particularly antipsychotics,[6-10] but the conditions of occurrence remain widely unknown. This review is focused on the following issues: comparison of the frequency, amount, and time frame of bodyweight gain of different atypical antipsychotics; characterisation of high risk groups; and the possible underlying pathomechanisms.

3. Literature Search

Publications concerning bodyweight gain and the atypical antipsychotics clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine were searched for using the database MEDLINE (from 1966 to March 2000). In an 'ancestry analysis' additional studies were obtained from the bibliographies of articles retrieved through the MEDLINE search.

4. Methodological Problems Associated with Comparison of Studies

The comparison of the different studies investigating bodyweight gain during treatment with atypical antipsychotics is hampered by some crucial methodological problems:

- study design (e.g. chart reviews, prospective or retrospective studies, randomised or open label studies and noncomparative or controlled studies)
- different recruitment procedures (e.g. highly selected samples, i.e. nonresponders to typical antipsychotics, inpatients in state hospitals)
- variation in patient characteristics (e.g. initial bodyweight and age)
- the use of different measures for bodyweight gain [e.g. lbs or kg, percentage bodyweight change, body-mass-index (BMI) or percentage thereof]
- presences of co-medication (often only mentioned in general terms)
- different duration of therapy.

The number or proportion of patients withdrawing from therapy or excluded from the study is reported in only a few studies. Furthermore, a comparison of the various drugs is limited by the lack of well accepted equivalent dosages. Moreover, it is an open question as to how much bodyweight gain is clinically relevant, since there is some evidence that patients with schizophrenia, particularly women, are more often obese than individuals without schizophrenia.[11-13] In view of spontaneous changes in bodyweight under different conditions [e.g. hospitalisation, depressive mood with low appetite, irregular food intake attributable to acute psychosis (thoughts of being poisoned)] an increase of more than 3kg or ≥5% within 12 weeks can be considered clinically relevant. However, it will be more

promising to calculate the increase as percentage of the BMI. Unfortunately, in most studies mentioned in this review, these measures are not given or cannot be calculated by the data presented.

5. Comparison of the Different Atypical Antipsychotics

5.1 Clozapine

Much clinical data on bodyweight gain has been documented for clozapine (table II).[9,10,12,14-24,51-53] The increase of bodyweight was significantly higher and occurred more frequently in patients receiving clozapine than those being treated with the typical antipsychotic drug haloperidol under the same conditions.[8,20,21] However, in many studies only patients with chronic schizophrenia whose condition had not responded to typical antipsychotics were included, so that these data could not be generalised.[15,18-22,25] Furthermore, the duration of treatment in many of these follow-up studies was rather long compared with investigations involving other atypical antipsychotics (≥52 *vs* ≤12 weeks).[19,21,22] Thus, in order to avoid bias attributable to the very different recruitment procedures, studies with such different designs were not compared in this review. However, there are also some data which show a marked increase in bodyweight after some weeks of treatment in patients treated with clozapine who were not highly selected.[9,14,16,17] The data compiled in table II suggest that bodyweight gain roughly correlates with the duration of treatment, particularly in the first 12 weeks of clozapine therapy. Thereafter, the increase in bodyweight abates.[19,20] The proportion of patients who are effected is rather high. More than 20% of all patients treated with clozapine experienced a bodyweight increase of more than 10% from baseline to follow-up at 12 weeks to 1 year.[10,16,18,20] Comprehensive statistical evaluations[11] as well as clinical comparisons[10] revealed that of all atypical antipsychotics clozapine induces the most pronounced bodyweight gain. There are some studies[16,18-20] showing a marked increase of bodyweight during clozapine therapy, e.g. after 52 weeks treatment with clozapine, 20% of patients gained at least 20% over their baseline bodyweight,[16] and a case report showing a bodyweight gain of up to 20kg within 2 months of clozapine treatment.[52]

5.2 Olanzapine

Olanzapine like clozapine has a pleotrophic pharmacology and affects the dopaminergic, serotonergic, muscarinic and adrenergic systems (see table I). Some recent studies[10,14,25-34,54,55] reported a significant increase in bodyweight in patients with schizophrenia treated with olanzapine (see table II). Bodyweight gain was more frequent and higher in patients treated with olanzapine than those receiving haloperidol[27,34] or risperidone (BMI within 8 weeks +1.3 *vs* 0.7 for olanzapine and risperidone, respectively)[29] under the same conditions. In a double-blind study, an association between bodyweight and increasing olanzapine dose was found, but no details were mentioned.[54] There is some evidence that olanzapine also induces marked bodyweight increase in children and adolescents[55] (table III).

5.3 Quetiapine

In a number of double-blind studies,[35-41] bodyweight gain (≥ 7%) occurred in 11 to 25% of the patients treated for 6 to 8 weeks with quetiapine compared with 4 to 5% of patients receiving placebo.[35,38,39] While in 1 study,[35] the mean bodyweight gain was 5.5kg after 6 weeks of treatment, in most other studies the mean bodyweight was less than 2kg.[36,37,41] Thus, the available results concerning bodyweight changes during quetiapine treatment showed a wide variation in the extent of bodyweight gain. However, the bodyweight gain that occurs during quetiapine treatment is higher than the gain occurring during haloperidol and placebo treatment.[35-39,41] There is some evidence from 1 study[56] with a rather small number of patients (n = 6) that children and adolescents also experience an increase in bodyweight during quetiapine treatment.

Table II. Comparison of studies describing bodyweight gain in adults attributable to treatment with atypical antipsychotics

Drug	Study design	Patient group	N (% of men)	Mean age (y) ± standard deviation	Dosage (mg/day) ± standard deviation	Duration of study (wks) ± standard deviation	% of patients with bodyweight gain	Definition of bodyweight gain	Mean bodyweight gain (kg) ± standard deviation	Bodyweight gain (%)	Reference
Clozapine	ol	SD, IP	11	37 ± 19	251 ± 177	4	ND	ND	2.3	3.3	14
	r	SD, IP	29	36 ± 12	379 ± 245	5 ± 4	45	≥5%	3.1 ± 3.7	4.1	9
	db[a]	SD, NR, C	43 (74)	36 ± 12	291	8	37	ND	2.7	3.5	15
	db	SD, OP	19	ND	410 ± 46	10 followed by 52 (ol follow-up study)	58 (at 52 wks)	≥10%	5.3	7.0	16
	r[a]	SD, C	99 (42)	38 ± 12	ND	12+	20	≥10%	5.3	4.1	17
	ol	SD, NR, IP	21 (62)	33	125	16	38	≥10%	6.3	8.9	18
	r	SD, C, IP, NR	36 (75)	35 ± 9	380 ± 135	26	75 42	≥ 4.5kg ≥ 9.0kg	7.0	10.6	12
	r	SD, IP	20 (100)	43 ± 1	ND	27 ± 8	45	≥10%	6.9 ± 0.8	8.8	10
	ol	SD, NR, IP & OP	51 (61)	40 ± 14	ND	52	70 (of the men)	ND	3.6 (wk 12); 7.5 (wk 52)	10.6	19
	ol	SD, NR, IP & OP	31	31 ± 11	241 ± 138	12 (followed by 52)	36	10%	3.5 ± 4.6 (wk 6)	ND	20
	ol	SD, NR	20 (65)	39 ± 9	206 ± 44	52+	32	≥5kg	ND	ND	21
	r	SD, NR	96 (59)	33 ± 10	440 ± 180	88	ND	ND	4.7	6.9	22
	r[a]	NS & SD, OP	121 (37)	42 ± 16	131 ± 99	128 ± 172	23	ND	ND	ND	23
	r[a]	SD & PY, IP	216 (85)	37	Mean 317	132 (range 26 to 600)	11 to 13	ND	ND	ND	24
Olanzapine	db, pc[a]	AM	70 (52)	40	Mean 15	3	ND	ND	1.7 (-0.4 for PL)	ND	25
	ol	SD	8	26 ± 6	14 ± 4	4	ND	ND	3.9	5.8	14
	db[a]	SD	102 (75)	38 and 39	1 and 10	6	ND	ND	2.2 (10 mg/day)	ND	26
	db[a]	SD	1312	38 ± 11	13.2 ± 5.8	6	ND	ND	1.9	ND	27
	db[a]	SD	196 (54)	39 ± 12	11.5 ± 5.9	6	ND	ND	5.0 ± 7.3	6.5	28
	db[a]	SD	189	39	12.4	8	ND	ND	3.9	6.5	29
	ol	SD & PY, IP	25 (84)	38 ± 12	13.8 ± 4.4	12	48	≥5kg	5.4	6.3	30
	ol	BAD	14	ND	14.1 ± 7.2	15 (range 4 to 31)	14	ND	ND	ND	31
	r	SD & PY	16	45 (range 24 to 75)	14 (range 10 to 30)	28 (range 8 to 40)	94	≥7%	10.0 (range 4 to 25.4)	12.2	32
	db[a]	SD	172 (65)	36 ± 11	17.2 ± 3.6	28	ND	ND	4.1 ± 5.9	ND	33

Continued next page

Table II. Contd.

Drug	Study design	Patient group	N (% of men)	Mean age (y) ± standard deviation	Dosage (mg/day) ± standard deviation	Duration of study (wks) ± standard deviation	% of patients with bodyweight gain	Definition of bodyweight gain	Mean bodyweight gain (kg) ± standard deviation	Bodyweight gain (%)	Reference
	r	SD, IP	13 (100)	45 ± 1	ND	73 ± 10	31	≥10%	6.8 ± 1.0	8.8	10
	db[b]	SD[c]	2418	ND	ND	Range 1 to 175	40	≥7%	ND	ND	34
Quetiapine	db, pc[a]	SD, C, IP	54 (89) [55 on PL]	36 ± 9 (37 ± 8 for PL)	307 (range 75 to 750)	6	25 (4 for PL)	≥7%	5.5 (0.5 for PL)	ND	35
	db[a]	SD, IP	221	37 ± 10	455 (range 150 to 750)	6	ND	ND	1.9	ND	36
	db[a]	SD	101	32 ± 10	Range 100 to 750	6	27	≥7%	1.8	ND	37
	db, pc[a]	SD, IP	258 (51 on PL) P: 51	Range 35 to 39	Range 75 to 750	6	11 to 17 (4 for PL)	≥7%	Range 0.9 to 2.9	ND	38
	db, pc[a]	ND	190 (76)	36 ± 9 37 ± 9	≤250 ≤750	6	16 25 (5 for PL)	≥7%	ND	ND	39
	db	SD, IP	618	Range 36 to 37	Range 50 to 450	6	50mg = 7 300mg = 13 450mg = 14	ND	ND	ND	40
	db[a]	SD, IP	143	38 ± 11	600	8	ND	ND	1.4	ND	41
Risperidone	r	SD, A, IP	15	35 ± 14	5.3	4 ± 2	40	≥5%	1.5 ± 2.9	2.4	9
	db	SD, C	1136	38	Range 1 to 12	8	ND	ND	0.3 (1 mg/day); 1.6 (8 mg/day)	ND	42
	db[a]	SD	188	41	4.8	8	ND	ND	2.0	2.4	29
	db, pc	ND	11	ND	Range 2 to 16	8	ND	ND	2.8 ± 4.2	3.9	43
	db[a]	SD, NR, C	43 (67)	38 ± 13	6.4	8	23	ND	1.1	ND	15
	db	SD,C	55 (73)	38	Range 5 to 15	8	39	ND	ND	ND	44
	db	SD, C IP	21 (71)	37 (range 21 to 66)	12 ± 1	12	ND	ND	2.0	2.8	45
	ol[a]	NR, IP	33 (70)	51 (range 25 to 66)	5.1 1-8	26	9	ND	ND	ND	46
	r	SD, IP	38 (100)	44 ± 1	ND	26 ± 6	13	>10%	5.0 ± 0.6	6.4	10
	db[a]	SD	167 (65)	36 ± 11	7.2 ± 2.7	28	ND	ND	2.3 ± 4.8	ND	33
	db	SD	177	40 ± 11	ND	51	ND	ND	2.3	2.8	47

Table 2 Cont.

5.4 Risperidone

Double-blind studies with risperidone produced varying results.[42-47,63-66] In a Finnish study,[64] no relevant changes in bodyweight occurred in patients with acute schizophrenia treated with risperidone. However, in another Scandinavian study,[44] 39% of patients with chronic schizophrenia gained bodyweight after 8 weeks of treatment with risperidone; this was about the twice the number of patients who increased in bodyweight while receiving perphenazine. In a Belgian study of patients with chronic schizophrenia,[45] the mean bodyweight of patients treated with risperidone for 12 weeks increased by 2kg which was similar to the increase of 1.4kg seen in patients treated with haloperidol. In further studies of risperidone in patients with chronic schizophrenia no significant changes in bodyweight were observed.[47,63] However, a meta-analysis[66] showed that bodyweight gain occurred more frequently in the patients receiving risperidone than in the patients receiving typical antipsychotics (31.2 *vs* 22.7%). Bodyweight increase has been shown to correlate with the prescribed dosage of risperidone.[42] Comparisons between risperidone and clozapine[9,10,15] or olanzapine[10,33] demonstrated significantly lower bodyweight gain in the risperidone recipients. Some reports have indicated a high risk of children and adolescents gaining bodyweight during treatment with risperidone[46,57-62] (table III). A study,[60] using monthly BMI measurements, demonstrated a significantly higher bodyweight gain in adolescents treated with risperidone than in those receiving typical antipsychotics or placebo.

5.5 Ziprasidone

There is a paucity of studies referring to bodyweight changes during ziprasidone treatment. In 2 placebo-controlled trials involving patients with acute schizophrenia or schizoaffective disorders treated with different dosages of ziprasidone (40 to 160 mg/day) only slight changes in bodyweight have been reported.[48,49] However, the duration of these studies was rather short (4[49] and 6[48] weeks).

Ziprasidone	db, pc[a]	SD, A	[106 (80 mg/day); 104 (160 mg/day); 92 (PL)] (72)	37 (80 mg/day); 36 (160 mg/day); 39 (PL)	80 and 160	6	ND	ND	1 (80 mg/day); 0 (160 mg/day); 0 (PL)	ND	48
	db, pc[a]	SD, A, IP	44 (40 mg/day); 47 (120 mg/day); 48 (PL)	41 (40 mg/day); 39 (120 mg/day); 39 (PL)	40 and 120	4	ND	ND	1 (40 mg/day)	ND	49
Zotepine	r[a]	SD, A, IP	19	35 ± 14	228 ± 126	5 ± 2	63	≥5%	4.3 ± 4.3	6.3	9
	db[a]	SD, A, IP	63 (48)	39	Range 150 to 300	8	ND	ND	2.3	ND	50

a Psychotropic co-medication mentioned.

b Combination of results from 4 studies.

c For 487 of the trial participants their condition was acute and they were treated as inpatients; no other details were provided for the remaining patients.

A = acute; **AM** = acute mania; **BAD** = bipolar affective disorder; **C** = chronic; **db** = double-blind; **IP** = inpatients; **ND** = no data; **NR** = nonresponder to typical antipsychotics; **NS** = patients without a schizophrenic or schizoaffective disorder; **ol** = open label; **OP** = outpatients; **PL** = placebo; **pc** = placebo-controlled; **PY** = patients with other psychoses; **r** = retrospective; **SD** = patients with a schizophrenic or schizoaffective disorder.

Table 3

5.6 Zotepine

Only a few studies referring to bodyweight changes during zotepine treatment have been performed to date.[9,50,67] These studies showed a marked increase of bodyweight during zotepine treatment, up to 17kg within 6 weeks.[67] The bodyweight gain was significantly higher in patients treated with zotepine than in patients treated with haloperidol.[9,50]

6. Bodyweight Gain in Relation to Pharmacological Properties

However, although some comparative studies[9,11,60] have demonstrated a significantly higher frequency and amount of bodyweight gain in patients with schizophrenia treated with an atypical antipsychotic than in those receiving a typical antipsychotic, the induction of bodyweight increase by atypical antipsychotics will be more convincing if some basic pharmacological criteria are met:

- a dose–effect relationship
- onset of bodyweight gain after the administration of the atypical antipsychotic drug.

6.1 Dose-Effect Relationship

Unfortunately, there are a lack of data to prove a relationship between the dosage of atypical antipsychotic and bodyweight gain, since only some studies reported results that confirm this association.[9,34,38-40,42,50] Bodyweight increase is associated with the prescribed dosage of olanzapine[34] and risperidone,[42] while the results of quetiapine studies[38-40] show no strong association.

6.2 Onset of Bodyweight after the Administration of an Atypical Antipsychotic Drug

Only a few of the cited studies[10,14,18,19,28,50,51,67] reported a baseline bodyweight measurement prior to the prescription of an atypical antipsychotic[19] therefore enabling the trial to show clear evidence of an induction of bodyweight increase by the administered atypical antipsychotic medication. Double-blind, placebo-controlled studies with olanzapine,[34] quetiapine,[35,38,39] and also risper-

Table III. Comparison of studies describing bodyweight gain in adolescents and children in the treatment with atypical antipsychotics

Drug	Study design	Patient group	N (% of males)	Mean age (y) ± standard deviation	Mean dosage (mg/day) ± standard deviation	Duration of study (wks)	% of patients with body-weight gain	Definition of bodyweight gain	Mean bodyweight gain (kg)	Mean bodyweight gain (%)	Reference
Olanzapine	ol	DD	8	20.9 (range 5 to 42)	7.8 ± 4.7	12	75	ND	8.3	13.2	55
Quetiapine	ol	AD	6 (100)	10.9 ± 3.3	Range 100 to 350	Range 4 to 16	50	>2kg	2.3 to 8.2	ND	56
Risperidone	ol	AD	11 (100)	18.3 (range 6 to 34)	ND	4	ND	ND	1.8	ND	57
	ol	AD	6	7.3	1.1	8	ND	ND	1.6 (range 0.5 to 3.1)	5.8	58
	ol	TD	7 (71)	12.9 ± 1.9	1.5 (range 1 to 2.5)	11	100	ND	Range 3.6 to 6.4	ND	59
	ol	AD	18 (84)	10.2 ± 3.7	1.8 ± 1.0	12	67	ND	8.1 ± 3.4 (range 4.5 to 16.0)	ND	60
	r	AD (n = 15) & DD (3)	18 (61)	14.1 ± 5.4	2.8 (range 0.5 to 10)	26	50	BMI ≥10%	8.6 ± 7.0	ND	61
	r	SD (n = 5), AD (12), DD (8) & O (13)	38 (84)	10.6 (range 5 to 17)	2.5 (range 0.5 to 10)	60 (range 4 to 140)	100	ND	10.4	27.3	62

AD = autistic disorders; **BMI** = body mass index; **db** = double-blind; **DD** = developmental disorders; **ND** = no data; **O** = other disorder; **ol** = open label; **r** = retrospective chart review; **SD** = patients with schizophrenic or schizoaffective disorders; **TD** = tic disorders.

idone[43] showed that bodyweight gain occurred significantly more frequently in patients receiving the atypical antipsychotics than in patients receiving placebo. These results support an association between induction of bodyweight gain and treatment with an atypical antipsychotic. Indirect support for this issue would be given by the relationship between the time of administration and the increase in bodyweight in patients treated with atypical antipsychotics. The last 2 columns of data presented in table II suggest such an association for at least the first 26 weeks of treatment.

In summary, although a comparison is severely limited by the different designs and recruitment procedures of the reviewed studies, the available data support the notion that the frequency as well as the amount of bodyweight gain is high in adult patients treated with 1 of the following drugs: olanzapine, clozapine, quetiapine and possibly zotepine. Moderate changes of bodyweight have been observed in adults during treatment with risperidone. There is some evidence that risperidone and olanzapine also induce marked bodyweight gain in children and adolescents. The available studies suggest that risperidone produces less bodyweight gain in adults than in children. The few available data concerning ziprasidone[48,49] show no significant bodyweight changes within the first 6 weeks of treatment. These considerations agree with comprehensive statistic evaluations[11] as well as with some clinical comparisons.[9,10]

7. Pathophysiology of Bodyweight Gain During the Medication with Atypical Antipsychotics

Many hypotheses have been suggested to explain the high rate of bodyweight gain in patients with psychiatric disorders during treatment with atypical antipsychotic drugs. However, it has to be mentioned that in some studies a remarkable proportion of the patients investigated lost bodyweight (5.0 to 30.6%),[19,34,42,44] while under the same conditions another subgroup significantly gained bodyweight (33.3 to 40.5%).[19,34,42,44]

7.1 Effect of Study Design or Recruitment Procedure

As in most of the cited studies only inpatients were investigated, the effects of institutionalisation must be taken into consideration. Inpatient treatment often leads to reduced activity, especially in patients who were overactive before. However, no correlation between the level of physical activity and patients' bodyweight could be found.[18,68] Additionally, meals are served regularly and food intake is controlled by the staff in the institutional setting. This setting may explain bodyweight gain, particularly in patients who neglected their food intake before because of illness. However, the effects of hospitalisation cannot sufficiently explain the differential effects of the various antipsychotic medications.

Moreover, patients with paranoid schizophrenia, who are often overactive and restless or restrict their food intake because of thoughts of being poisoned, should gain more bodyweight than patients with residual schizophrenia, who in contrast, often experience slowness and lack of drive. Unfortunately, there are very few data concerning this issue. However, patients with residual schizophrenia often experience obesity.[9,13] So in patients with schizophrenia, bodyweight changes may be attributable to the present symptomatology (e.g. inactive lifestyle or thoughts of being poisoned). Thus, this raises the question of whether bodyweight increase during medication with atypical antipsychotic occurs more frequently in patients with schizophrenia than in patients with other psychiatric disorders. The few published data on patients with other diagnoses such as bipolar-affective disorder[31] or mania[25] have yielded no conclusive results.

7.2 Effect of Specific Pharmacological Profile of Atypical Antipsychotics

In view of the differential drug effects on bodyweight as presented in this review the pharmacological profile (see table I) of the administered antipsychotics has to be taken into consideration:

- antagonistic effects on dopamine receptors

- anticholinergic effects
- antihistaminergic effects
- antagonistic effects on serotonin receptors.

It is noteworthy that in nearly all cited studies a psychotropic co-medication (e.g. lorazepam or other benzodiazepines) was allowed (as indicated in tables II and III). However, there was no evidence that concomitant medication has any influence on bodyweight gain.[20,24,50,60]

7.2.1 Antagonistic Effects on Dopamine Receptors

The antagonistic effect of the atypical antipsychotic on the D_2 receptor is considered to be most important in producing an antipsychotic effect. However, positron emission tomography studies[69] revealed that some atypical antipsychotics, such as clozapine, show only a moderate occupation of the D_2 receptor *in vivo* (<70%), although they are well documented to increase bodyweight. Thus, there is no clear evidence that bodyweight gain corresponds with the D_2 receptor affinity of these agents although dopamine receptors are considered to be involved in feeding regulation.

7.2.2 Anticholinergic Effects

Many drugs that have an anticholinergic effect may induce a dry mouth and thereby stimulate thirst. Therefore, patients complaining of a dry mouth may drink excessively. If they consume large quantities of high calorie drinks, they may gain bodyweight. Receptor studies revealed that clozapine, olanzapine, and zotepine have a high affinity at the muscarinic acetylcholine M_1 receptor. However, thus far no relationship between bodyweight gain and an anticholinergic co-medication (like biperidene) has been found in studies with typical antipsychotics[9] or with clozapine.[24] Although clozapine has a high affinity for M_1 receptors, it frequently causes hypersalivation. The underlying mechanism remains unclear (possible effect on M_4 receptors?).

7.2.3 Antihistaminergic Effects

Some atypical antipsychotics like clozapine, olanzapine, quetiapine, and zotepine show a high affinity for the histamine H_1 receptor (table I). These agents have sedative effects. Sedation may induce bodyweight gain by reduced mobility, if calorie intake is not decreased. The relative receptor affinities of the atypical antipsychotics for the H_1 receptor appear to be a robust correlate of bodyweight gain.

7.2.4 Antagonistic Effects on Serotonin Receptors

As serotonin plays an important role in the regulation of appetite and food intake[8,68-72] serotonin-antagonistic effects are discussed in the literature to explain bodyweight changes related to antipsychotic treatment.[6,9,10] Drugs with a serotonergic effect such as fenfluramine or fluoxetine can induce a decrease in bodyweight.[73,74] However, it remains speculative as to which serotonin receptor type is responsible for stimulating food intake and bodyweight gain. Animal experiments revealed a prominent role of the 5-HT_{2c} receptor in the regulation of food intake.[75,76] In human studies some patients reported increased appetite during the treatment with an atypical antipsychotic drugs such as olanzapine,[55,27] while some others complained of a decreased appetite.[27,45] However, some studies[6,9,10,14] showed a marked bodyweight gain predominately in patients treated with antipsychotics that have an antagonistic effect on the 5-HT_2 receptor.

In summary, antipsychotics that have an antagonistic effect on the D_2 as well as 5-HT_2 receptor as indicated by a low 5-HT_2 to D_2 ratio and/or an antihistaminergic effect frequently induce bodyweight gain.

7.3 Other Factors Contributing to Bodyweight Gain Possibly Induced by Atypical Antipsychotics

Some studies revealed that most atypical antipsychotics, particularly clozapine,[17] olanzapine,[34] quetiapine,[36,39] risperidone,[42,66] and also zotepine[50] show frequent gastrointestinal adverse effects, particularly constipation, and upper gastrointestinal symptoms, reflecting the high affinity of these drugs for cholinergic receptors. Constipation may lead to bodyweight gain, but up to now there is no support for such an association.

Moreover, there is some evidence that olanzapine and clozapine are associated with *de novo* diabetes mellitus in persons with risk factors for diabetes

mellitus[77,78] and with severe exacerbation of pre-existing diabetes mellitus. Clozapine seems to induce glucose intolerance or elevated insulin serum levels, more frequently than typical antipsychotics.[79] However, the change in glycaemic control caused by clozapine was not significantly related to bodyweight gain.[80]

Some recent studies have shown that clozapine,[77,80] olanzapine,[30] and ziprasidone[49] may induce an increase in serum triglyceride levels. There was a strong association between bodyweight change and the change in triglyceride level.[30] Ziprasidone treatment may also be associated with an increase in the plasma level of cholesterol.[48,49] However, up to now there are no studies clearly indicating an association between bodyweight gain and increased serum levels of cholesterol or triglycerides induced by atypical antipsychotics.

Two recent studies[14,81] revealed that clozapine and olanzapine increase the serum leptin levels significantly. Leptin is produced by fat cells and is presumed to signal the size of the adipose tissue to the brain. Overeating is associated with elevated leptin secretion. Thus, the increased secretion may have an important impact on bodyweight gain in patients treated with atypical antipsychotics.

7.3.1 Smoking

Approximately 80% of individuals with schizophrenia are smokers.[82] The cessation of smoking is strongly associated with bodyweight gain. Thus, the question is raised as to whether changes in smoking habits induced by use of a prescribed antipsychotic contribute to bodyweight gain during treatment with an atypical antipsychotic. There is some evidence that clozapine may alter smoking behaviour in patients with chronic schizophrenia.[83,84] A significant decrease in reported daily cigarette use was observed during clozapine treatment;[83] such a decrease might contribute to bodyweight gain. Unfortunately, no data on the effect of other atypical antipsychotics on smoking habits are available thus far. However, a reduction in cigarette smoking induced by atypical antipsychotics may be an important contributing factor for bodyweight gain in these patients.

8. Timeframe of Bodyweight Gain

A very serious question in context with bodyweight gain of patients treated with atypical antipsychotics is whether there is correlation between the increase in bodyweight and the duration of treatment. In view of the importance of this issue, the data in tables II and III have been presented according to the duration of treatment. Bodyweight gain most frequently occurred in the first 4 to 12 weeks of treatment[16,19,20] (see also tables II and III for additional references). However, a further increase in bodyweight (maximum 30%) was observed during long term follow-up.[16,19,20] In particular, patients treated with clozapine and olanzapine appeared to gain bodyweight over a prolonged period of time, whereas patients treated with risperidone had a more limited period of bodyweight gain.[10]

9. Relation to Treatment Benefit

A very important question is whether treatment benefit is related to bodyweight gain.[85] Some authors[16,18,20] noted a tendency for an inverse correlation between bodyweight gain during clozapine treatment and reduction of the Brief Psychiatric Rating Scale (BPRS) score. Similar results were reported for olanzapine. 60% of the patients gaining bodyweight during olanzapine treatment also had a reduction in their BPRS score.[32] However, bodyweight gain was not significantly correlated with improvements in either positive or negative symptoms.[16] Nevertheless, in the pre-antipsychotic era bodyweight gain was often considered as indicator of amelioration in patients with schizophrenia.

10. Possible At-Risk Groups

In view of the fact that not all patients treated with atypical antipsychotics gain bodyweight, possible risk factors have to be evaluated. No age or gender difference was found in studies of olanzapine.[27,34] Moreover, some authors[19,53] found that gender, age, and duration of illness did not predict bodyweight gain in patients treated with clozapine at follow-up after ≥ 12 months, while bodyweight

increase within the first 3 months of treatment correlated with bodyweight gain at 12 months.

As shown in table III, children are also at risk of gaining bodyweight. There is some evidence[9] that previously treated patients gain bodyweight significantly more frequently than those patients who have not previously received an antipsychotic. Moreover, those patients observed for more than 1 treatment episode show a lower increase in bodyweight in later treatment episodes.[9] However, older patients with schizophrenia (>55 years) also gain bodyweight during clozapine treatment.[86]

In some studies,[9,20,27,34] lower bodyweight at the beginning of the treatment had a significant influence on bodyweight gain; bodyweight increase was most marked in those patients who were underweight at the beginning of treatment. However, no correlation between BMI at baseline and bodyweight gain was found in another study.[10]

11. Therapeutic Interventions

Since on the one hand there is some evidence for an association between therapeutic efficacy and bodyweight gain, and on the other hand obesity often causes manifold medical consequences, approaches for therapeutic interventions against bodyweight gain during the treatment with atypical antipsychotics are much needed. Unfortunately, only a few investigations[10,19,61,87] showing the course of bodyweight gain and the efficacy of therapeutic interventions are available up to now. Despite behavioural interventions (e.g. nutritional consultation, suggested exercise regimen) bodyweight gain with clozapine, but not olanzapine or risperidone, appears to persist.[10] Thus, further strategies to manage bodyweight gain induced by antipsychotic medication[87] have to be investigated in future trials.

Apart from cognitive–behavioural interventions requiring a high compliance by the patient, pharmacological interventions should be considered. The serotoninergic agent fenfluramine was administered to patients with schizophrenia who were obese and bodyweight reduction was achieved.[88] Perhaps the combination of an atypical antipsychotic and a serotonin reuptake inhibiting drug which is frequently prescribed to treat predominately negative schizophrenic symptoms may help to avoid severe bodyweight in patients with chronic schizophrenia. However, no data are available. From a theoretical view these combinations may lead to a reduction in antipsychotic efficacy, since the antiserotonergic activity which is considered to account for the 'atypical' effects of some antipsychotics may be antagonised by the serotonergic action of serotonin reuptake inhibitors or fenfluramine.

12. Complications

There is some evidence that many patients with chronic schizophrenia experience obesity,[8,11] which is associated with an increase in morbidity. Obesity is well known to be strongly associated with numerous health problems such as hypertension, heart disease and diabetes mellitus.[89] Even small amounts of bodyweight gain can lead to serious health issues over time.[90] Since patients with schizophrenia often show abnormal behaviour (such as excessive smoking, alcohol and substance abuse, and lack of exercise) the question must be raised as to whether bad dietary habits contribute to bodyweight gain. This critical question challenges further investigations. However, bad dietary habits cannot sufficiently explain the differential effects of various antipsychotic medications on bodyweight. Moreover, only a proportion of the patients treated with atypical antipsychotics reported increased appetite during the medication.[27,34,55]

Bodyweight gain associated with the use of atypical antipsychotics not only can contribute to the onset of secondary problems for patients, but also may lead to noncompliance, another factor that can put patients at risk.[91] Thus, there is a 'therapeutic dilemma' in planning treatment strategies for patients with schizophrenia: the high risk of bodyweight gain during the therapy with atypical antipsychotics on the one hand, the high risk of severe EPS during therapy with typical antipsychotics on the other hand. Both adverse effects frequently occur early in treatment and can reduce patients' compliance, particularly for long term treatment. As is known from the experience with lithium treatment,

bodyweight gain is associated with a high rate of refusal of any further medication.[92] Moreover, compliance with prescribed antipsychotics is generally rather low.[93]

13. Future Studies

The recent data strongly suggest an association between atypical antipsychotics and bodyweight gain, but some important issues need further evaluation. Thus, future studies with atypical antipsychotics should be planned in order to provide further data on the following questions.

- Are younger patients at increased risk of bodyweight gain?
- Are individuals who are antipsychotic-therapy naive at increased risk of experiencing bodyweight gain?
- Is bodyweight gain associated with the degree of therapeutic benefit?
- Which interventions are effective in reducing bodyweight gain induced by an atypical antipsychotics?
- Is there an association between bodyweight gain and leptin, insulin or growth hormone serum levels or the serum concentration of the atypical antipsychotics?

Furthermore, it seems worthwhile to investigate if atypical antipsychotics with a bodyweight gain–inducing effect could be used in the therapy of patients with eating disorders.

14. Conclusions

This comparative review shows that clozapine, olanzapine and quetiapine induce an increase of bodyweight to a higher amount and more frequently than risperidone. The few available data concerning ziprasidone and zotepine and bodyweight gain are insufficient to draw final conclusions, but there is some evidence that, apart from ziprasidone, all atypical antipsychotics can induce bodyweight gain. Bodyweight gain most frequently occurs within the first 6 to 12 weeks of treatment with an atypical antipsychotic. Some evidence indicates that patients, particularly young patients, who are underweight at the beginning of treatment are at increased risk of experiencing bodyweight gain, if treated with atypical antipsychotics. Bodyweight gain induced by atypical antipsychotics seems to be largely irreversible without use of a rigorous diet. In view of the high rate of medical complications associated with obesity, patients treated with atypical antipsychotics should be weighed at least every 2 weeks. If bodyweight gain occurs (>2kg within 2 weeks), a strict dietary regimen should be initiated immediately.

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