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Effetti diabetogeni dei farmaci psichiatrici

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Conflitti di interessi: nessuno

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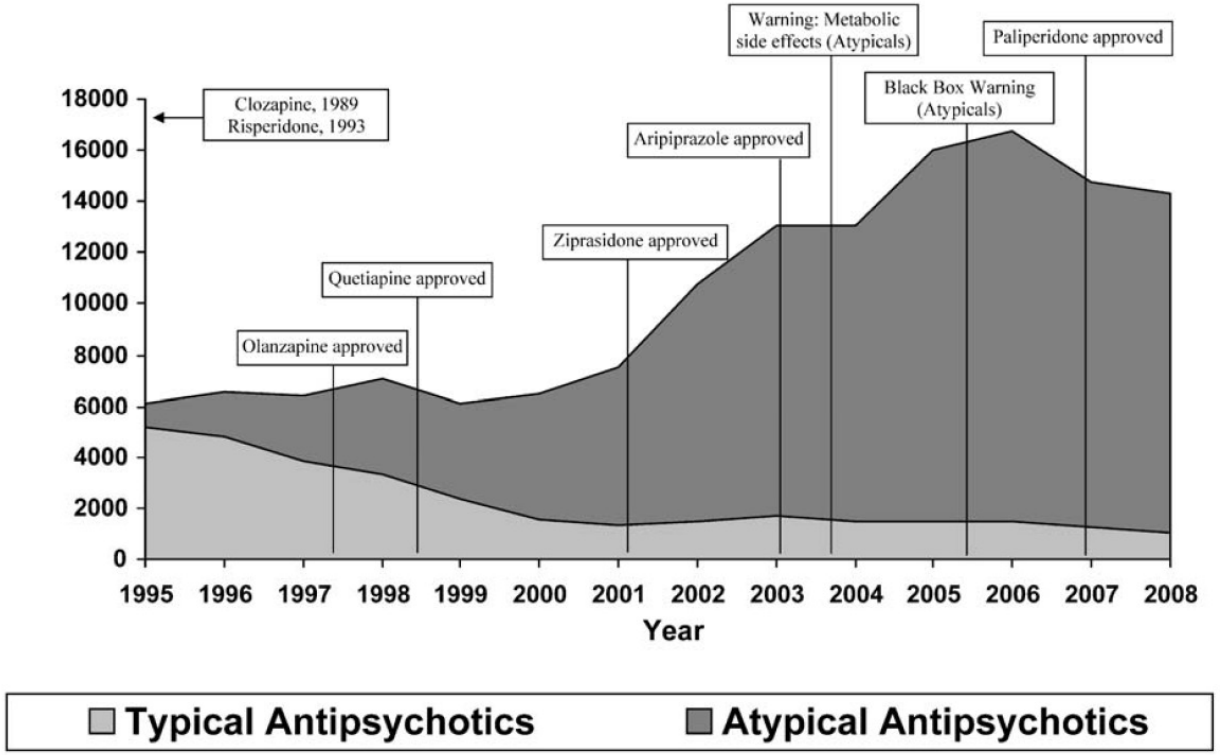
ORIGINAL REPORT

Increasing off-label use of antipsychotic medications in the United States, 1995–2008

G. C. Alexander[1,2,3]*, S. A. Gallagher[4], A. Mascola[5], R. M. Moloney[1] and R. S. Stafford[6]



*Source: IMS Health National Disease and Therapeutic Index™, 1995-2008

Figure 2. Aggregate use of typical and atypical antipsychotics, 1995–2008.* *Source: IMS health national disease and therapeutic index™, 1995–2008

Prescribing pattern of antipsychotic drugs in the Italian general population 2000–2005: a focus on elderly with dementia

Gianluca Trifirò[a,b,c], Giovanna Sini[d], Miriam C.J.M. Sturkenboom[c], Nicola Vanacore[e], Giampiero Mazzaglia[d], Achille P. Caputi[a,b], Claudio Cricelli[d], Ovidio Brignoli[d], Eugenio Aguglia[f], Giovanni Biggio[g] and Fabio Samani[d]

International Clinical Psychopharmacology 2010, 25:22–28

Antipsicotici in 1,5% della popolazione generale

Table 1 Prevalence of antipsychotic drug use (per 1000 inhabitants per year) in the Italian general population during the years 2000–2005

	2000		2001		2002		2003		2004		2005	
Antipsychotic type	No. of users	Prevalence	No. of users	Prevalence	No. of users	Prevalence	No. of users	Prevalence	No. of users	Prevalence	No. of users	Prevalence
Atypicals	655	1.28	1476	2.75	1781	3.26	1880	3.41	1884	3.34	1952	3.36
Typicals	7643	14.93	8411	15.65	7934	14.53	6283	11.40	6180	10.97	6356	10.94
Phenotiazines	1933	3.78	2092	3.89	1910	3.50	1843	3.34	1993	3.54	2038	3.51
Butyrophenones	1511	2.95	1725	3.21	1866	3.42	1887	3.42	2074	3.68	2299	3.96
Benzamides	4414	8.62	4827	8.98	4291	7.86	2579	4.68	2197	3.90	2105	3.62
Others	488	0.95	546	1.02	578	1.06	582	1.06	548	0.97	624	1.07
Total	8036	15.70	9363	17.42	9151	16.76	7607	13.80	7527	13.36	7749	13.34

JMCP
JOURNAL OF MANAGED CARE PHARMACY

Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics

Alicia R. Maher, MD
George Theodore, PhD

TABLE 1 Currently Approved Atypical Antipsychotics

Drug	Date of Original FDA Approval[a]
Clozapine[b]	September 26,1989
Risperidone	December 29,1993
Olanzapine	September 30,1996
Quetiapine	September 27,1997
Ziprasidone	February 5, 2001
Aripiprazole	November 15, 2002
Paliperidone[c]	December 19, 2006
Iloperidone[c]	May 6, 2009
Asenapine[c]	August 13, 2009

[a]*Derived from FDA information at http://www.accessdata.fda.gov.*
[b]*Excluded from this comparative effectiveness review.*
[c]*No evidence of off-label use was discovered for these drugs.*
FDA= U.S. Food and Drug Administration.

TABLE 3 Efficacy of Atypical Antipsychotics by Condition and Strength of Evidence

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety					
Generalized anxiety disorder	O	-	++	-	-
Social phobia	O	+	-	O	O
Attention-deficit hyperactivity disorder					
No co-occurring disorders	O	O	O	+	O
Bipolar children	-	O	O	O	O
Mentally retarded children	O	O	O	+	O
Dementia					
Overall	++	+	+	++	O
Psychosis	+	+-	+-	++	O
Agitation	+	++	+-	++	O
Depression					
MDD augmentation of SSRI/SNRI	++[a]	+[a]	++[a]	++	+
MDD monotherapy	O	-	++	O	O
Eating disorders	O	--	-	O	O
Insomnia	O	O	-	O	O
Obsessive-compulsive disorder					
Augmentation of SSRI	O	+	--	++	-
Augmentation of citalopram	O	O	+	+	O
Personality disorder					
Borderline	+	+-	+	O	-
Schizotypal	O	O	O	+-	O
Post-traumatic stress disorder	O	+-	+	++	O
Substance abuse					
Alcohol	--	-	-	O	O
Cocaine	O	-	O	-	O
Methamphetamine	-	O	O	O	O
Methadone clients	O	O	O	-	O
Tourette's syndrome	O	O	O	+	-

Symbol legend: For strength of evidence: ++ = moderate or high evidence of efficacy; + = low or very low evidence of efficacy; +- = mixed results; - = low or very low evidence of inefficacy; -- = moderate or high evidence of inefficacy; O = no trials.
Source: Maglione M, Ruelaz Maher A, Hu J, et al. Off-label use of atypical antipsychotics: an update. AHRQ comparative effectiveness review no. 43. September 2011.[1]
[a]*FDA approved for this indication.*
FDA= U.S. Food and Drug Administration; MDD= major depressive disorder; SNRI= serotonin norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor.

OPINION

The 'atypicality' of antipsychotics: a concept re-examined and re-defined

Gerhard Gründer, Hanns Hippius and Arvid Carlsson

Abstract | Recent clinical trials have raised questions over the perceived advantages of second-generation 'atypical' antipsychotics over those from the first generation. An atypical antipsychotic in its original sense is one that lacks extrapyramidal side effects. However, the addition of other clinical features to the original concept of atypicality, such as efficacy against negative and cognitive symptoms, seems to have become a feature of searches for novel antipsychotics in the past two decades. Although this approach has led to some therapeutic advances, we propose that it has also hampered antipsychotic drug research and that reframing the concept of atypicality could have a key role in making genuine breakthroughs in schizophrenia therapy.

NATURE REVIEWS | DRUG DISCOVERY

VOLUME 8 | MARCH 2009 | 197

CATALESSIA
Disturbo psicomotorio del tono muscolare e dell'iniziativa motoria, caratterizzato da plasticità e fissità degli atteggiamenti, per cui il paziente conserva le posizioni che gli vengono imposte, insieme all'incapacità di muoversi spontaneamente, determinando così uno stato di passività anche assoluta.

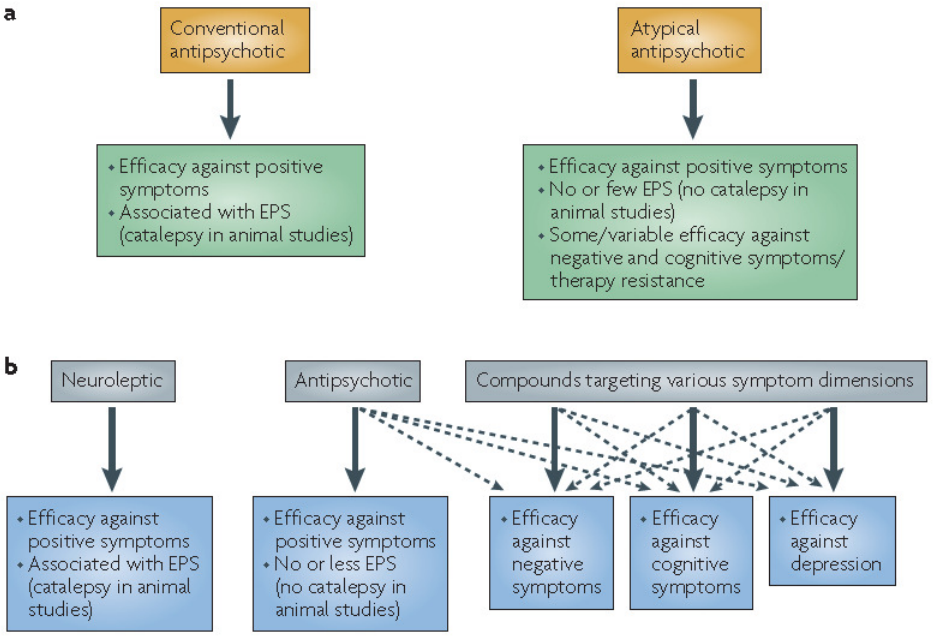


Figure 1 | **Current and proposed classification of compounds for the treatment of schizophrenia.** **a** | The widely accepted classification of antipsychotics assumes that there is a categorical difference between first-generation antipsychotics (conventional antipsychotics) and second-generation antipsychotics (atypical antipsychotics). Although the original concept of an atypical antipsychotic included only the lack of extrapyramidal side effects (EPS), it seems that it has been substantially broadened in the last decade to include aspects such as efficacy against negative and cognitive symptoms, lack of prolactin elevation and efficacy in treatment-resistant patients. **b** | Here, we suggest to restrict the term antipsychotic to compounds that induce no or very few EPS (thus, to replace the 'atypical antipsychotic' in its classical sense by the 'naked' term 'antipsychotic') and to classify compounds that induce EPS (or catalepsy in animals) as 'neuroleptics'. Symptom dimensions other than positive symptoms should be targeted by drugs that are specifically designed for this purpose. Multi-target drugs might be effective against multiple symptom dimensions, and a single symptom dimension might be targeted by drugs acting at various molecular targets (dashed arrows). Furthermore, the available antipsychotics might be effective (to a variable degree) against symptom dimensions other than positive symptoms depending on their molecular profile. Thus, any given drug is characterized by its individual, molecularly defined 'efficacy profile'.

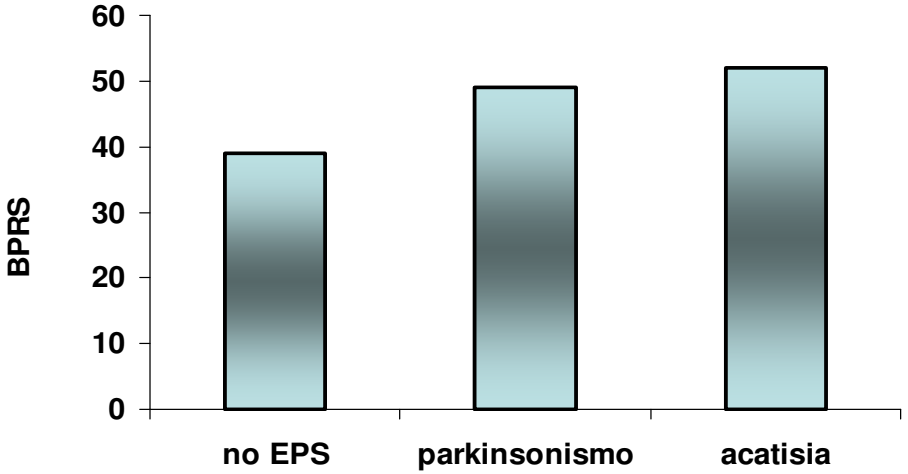
HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol. Clin. Exp. **15**, 79–85 (2000)

Extrapyramidal Symptoms and Residual Psychopathology with Low-Dose Neuroleptics

DOMENICO BERARDI*, ANNALISA GIANNELLI, ROBERTO BISCIONE and GIUSEPPE FERRARI
Institute of Psychiatry, Bologna University, Bologna, Italy

Residual psychopathology associated with EPS has been mainly assessed in experimental studies where neuroleptics were administered at standard, fixed dosages. The present study evaluates residual psychopathology in 69 schizophrenic patients treated with moderate, flexible doses of neuroleptics (430 mg eq. CPZ) at the out-patient Community Mental Health Services (CMHSs) in Bologna. Akathisia was present in 27·5 per cent of patients and parkinsonism in 27·5 per cent. A more severe psychopathological state was associated with both side-effects, as seen by significantly higher BPRS global scores. This severity was due to tension and anxiety–depression symptoms in patients with akathisia and to negative symptomatology in patients with parkinsonism, as shown by significant associations with BPRS subscales ANS-DEP and NEG, respectively. In conclusion, the present study underlines that EPS are frequent even in an out-patient setting where moderate neuroleptic doses are employed, and more importantly shows that in these conditions, the residual psychopathology resulting from EPS is clinically very significant.

KEY WORDS — akathisia; parkinsonism; antipsychotic drugs; residual psychopathology; subjective effect; out-patients; antipsychotic low-doses



- Diminuita spontaneità
- Espressione e modo di esprimersi rigide
- Apatia
- Difficoltà ad iniziare attività quotidiane
- Gestualità coartata
- Effetto zombie

- Sensazione di irrequietezza interiore
- Compulsione al movimento
- Ansia
- Irritabilità
- Impulsività

Clozapine effectiveness in a psychiatric service in Italy

D Berardi[1], M Troia[1], M Dell'Atti[1], C Bartoletti[2], C Cantaroni[1], G Ferrari[1]

[1] *University of Bologna, Department of Psychiatry, 'P Ottonello', Viale C Pepoli, 5, 40123, Bologna;*
[2] *Mental Health Service 'Villa Olimpia', AUSL Bologna, Italy*

(Received 16 June 1997; final version 20 April 1998; accepted 28 April 1998)

Eur Psychiatry 1998 ; 13 : 317-9

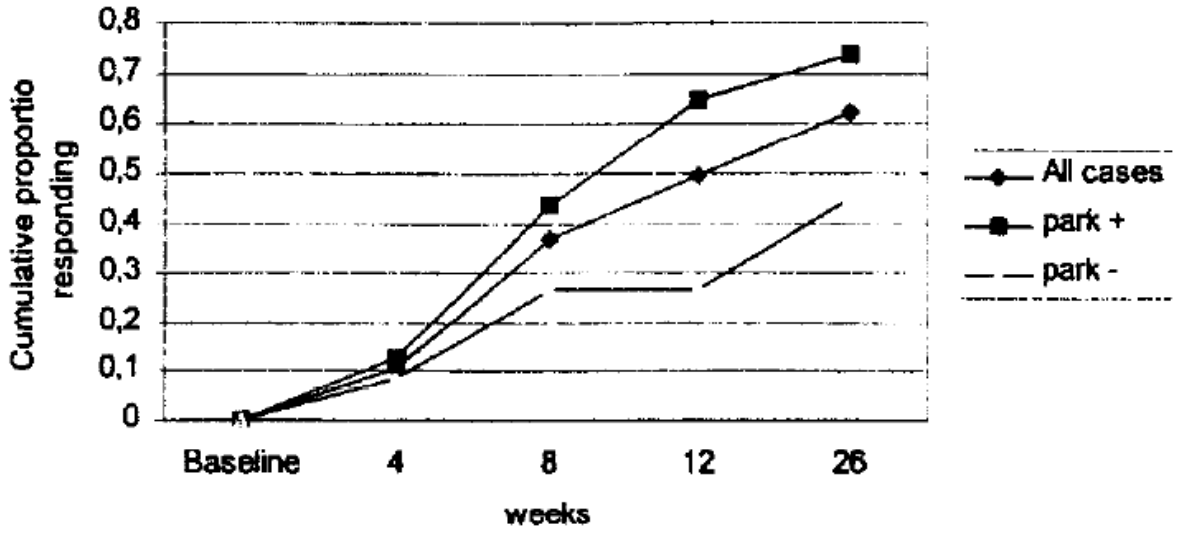


Fig 1. Time course of clozapina treatment and rate of response seen in the whole sample and in patients with or without parkinsonism.

Molecular Psychiatry (2008) 13, 918–929
 1359-4184/08 $30.00
www.nature.com/mp

FEATURE REVIEW

Antipsychotic drug mechanisms: links between therapeutic effects, metabolic side effects and the insulin signaling pathway

RR Girgis[1,2], JA Javitch[1,2] and JA Lieberman[1,2]

The exact therapeutic mechanism of action of antipsychotic drugs remains unclear. Recent evidence has shown that second-generation antipsychotic drugs (SGAs) are differentially associated with metabolic side effects compared to first-generation antipsychotic drugs (FGAs). Their proclivity to cause metabolic disturbances correlates, to some degree, with their comparative efficacy. This is particularly the case for clozapine and olanzapine. In addition, the insulin signaling pathway is vital for normal brain development and function. Abnormalities of this pathway have been found in persons with schizophrenia and antipsychotic drugs may ameliorate some of these alterations. This prompted us to hypothesize that the therapeutic antipsychotic and adverse metabolic effects of antipsychotic drugs might be related to a common pharmacologic mechanism. This article reviews insulin metabolism in the brain and related abnormalities associated with schizophrenia with the goals of gaining insight into antipsychotic drug effects and possibly also into the pathophysiology of schizophrenia. te about one potential mechanism of action (that is, functional selectivity) sistent with the data reviewed herein and make suggestions for the future s required before a therapeutic agent based on these data can be realized.
/ (2008) **13,** 918–929; doi:10.1038/mp.2008.40; published online 15 April 2008

Table 1 Comparisons between second-generation antipsychotics on effectiveness, degree of metabolic disturbances and magnitude of effects on glycogen synthase kinase

Clinical and biochemical measures	*Comparisons between SGAs*
Effectiveness	Clz > Olz ⩾ Risp ≃ Quet ≃ Zip ≃ Ari
Degree of metabolic disturbances	Clz ⩾ Olz > Risp ≃ Quet ⩾ Zip ≃ Ari
Magnitude of effects on GSK	Clz ≃ Olz > Risp ≃ Quet ⩾ Zip

Abbreviations: Ari, aripiprazole; Clz, clozapine; GSK, glycogen synthase kinase; Olz, olanzapine; Quet, quetiapine; Risp, risperidone; SGAs, second-generation antipsychotic drugs; Zip, ziprasidone.

National Institute for Health and Clinical Excellence

Schizophrenia

Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care

Issued: March 2009

NICE clinical guideline 82
guidance.nice.org.uk/cg82

Pharmacological interventions

- For people with newly diagnosed schizophrenia, offer oral antipsychotic medication. Provide information and discuss the benefits and side-effect profile of each drug with the service user. The choice of drug should be made by the service user and healthcare professional together, considering:
  - the relative potential of individual antipsychotic drugs to cause extrapyramidal side effects (including akathisia), metabolic side effects (including weight gain) and other side effects (including unpleasant subjective experiences)
  - the views of the carer where the service user agrees.
- Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

Lancet 2009; 373: 31–41

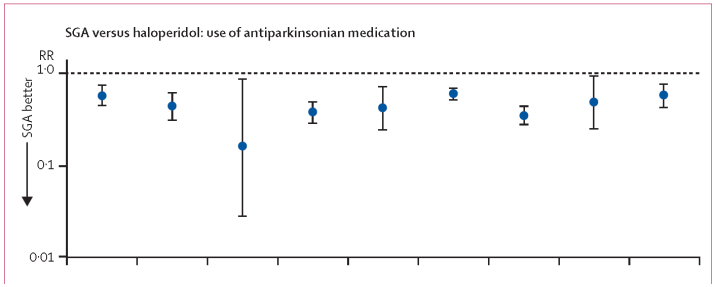


Figure 4: **Extrapyramidal side-effects**
Data are relative risk (RR; 95% CI). SGA=second-generation antipsychotic drug. FGA=first-generation antipsychotic drug. *Use of antiparkinsonian medication.

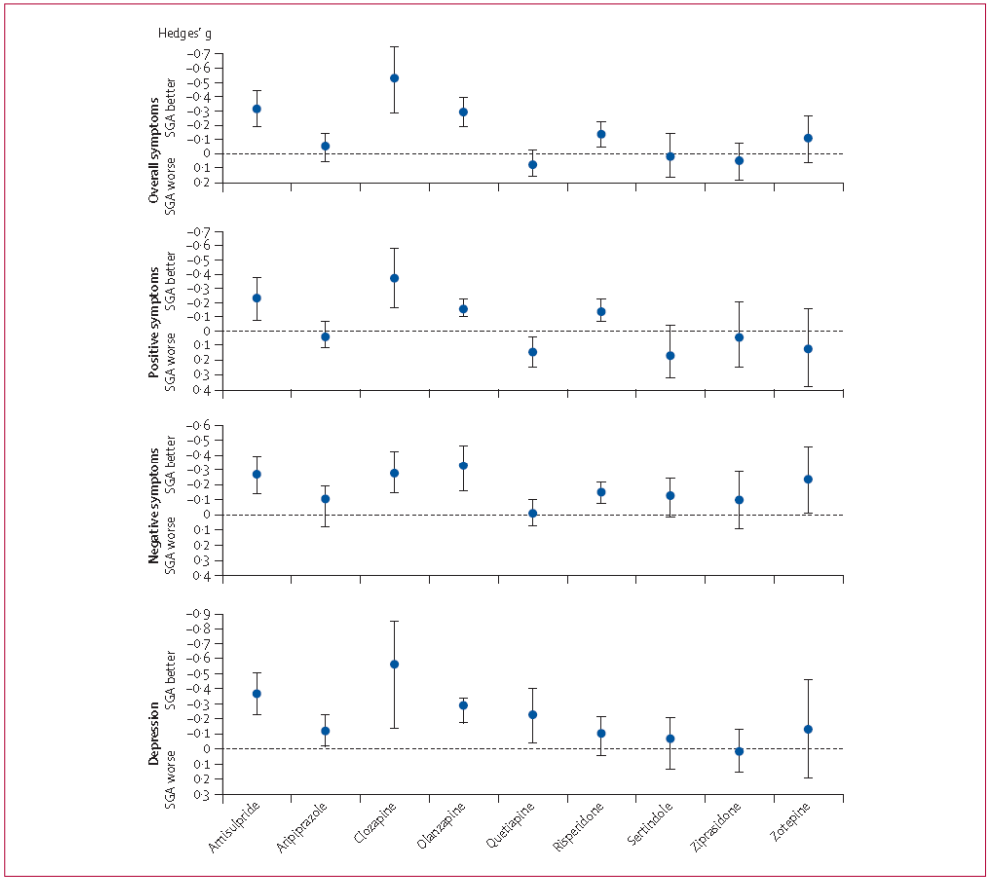


Figure 2: **Second-generation versus first-generation antipsychotic drugs—efficacy in various domains**
Data are Hedges' g (95% CI). Note that the results are significant at p<0·05 if the 95% CIs do not overlap the x axis. SGA=second-generation antipsychotic drug.

Clinical Neuropsychiatry (2007) 4, 4, 152-159

- 30 pazienti precedentemente in trattamento con FGA o SGA,
- 9 drug-naive

THE TIME COURSE OF SECOND GENERATION ANTIPSYCHOTIC METABOLIC SIDE EFFECTS: RESULTS FROM A ONE-YEAR PROSPECTIVE EVALUATION IN A COMMUNITY MENTAL HEALTH SERVICE

Ilaria Tarricone, Beatrice Ferrari Gozzi, Daniela Grieco, Beatrice Berti, Stefano Biagini, Alessandro Serretti, Marco Menchetti, Renato Pasquali, Domenico Berardi

Table 3. *Changes in metabolic mean values after 1, 6 and 12 months*

	Baseline	1 month	6 months	12 months	f	df	p*
BMI**	27.2±4.3	27.9±4.2	29.0±4.7	29.1±4.7	12.1	3(75)	**<0.0001**
Glucose[1]mg/dl	91.0±17.3	88.6±15.2	88.6±12.0	92.0±29.5	0.7	3(69)	0.58
Cholesterolmg/dl	203.6±37.5	212.7±45.7	218.7±43.3	209.5±41.3	2.4	3(99)	0.68
Triglycerides[2]mg/dl	132.2±58.3	161.8±89.8	134.3±72.1	141.7±79.1	1.9	3(78)	0.14

*significance for 0-12 months means comparison

** Post Hoc Analysis :

-baseline vs 6 months: p= 0.000035

-1 month vs 6 months p=0. 012986

-1month vs 12 months p=0.006090

[1] mean calculated without the glycaemia level of two patients treated with hypoglycaemic agents

[2] mean calculated without the triglyceride level of one patient

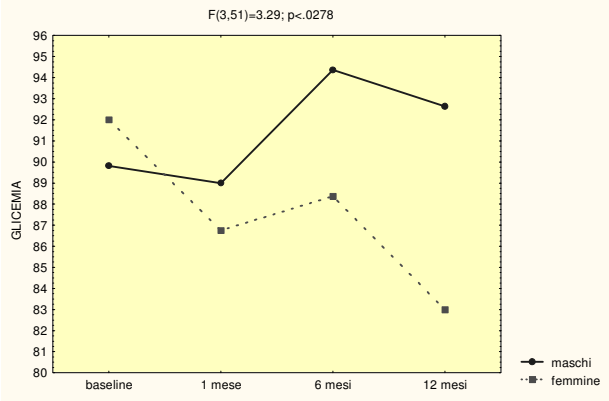
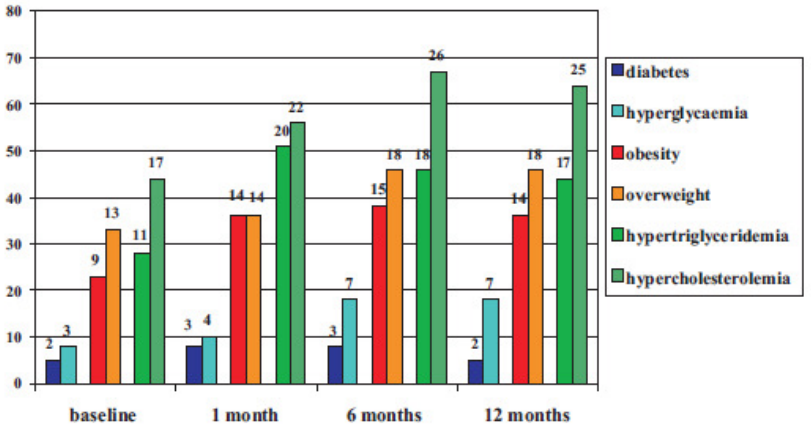


Figure 1. *Prevalence of metabolic disorders at baseline, 1, 6 and 12 months*



Psychological Medicine (2010), **40**, 187–200. © Cambridge University Press 2009
doi:10.1017/S0033291709990407

REVIEW ARTICLE

Weight gain in antipsychotic-naive patients: a review and meta-analysis

I. Tarricone*, B. Ferrari Gozzi, A. Serretti, D. Grieco and D. Berardi

Institute of Psychiatry, Bologna University, Italy

Background. Weight gain is a long-recognized side-effect of antipsychotic (AP) drugs and a major health concern in the treatment of psychosis. The strength of the causal relationship between AP drug exposure and weight gain can only be gauged by a drugs trial conducted on AP-naive patients.

Method. We conducted a review of the literature regarding the amount of weight gain induced by APs in AP-naive patients and carried out a meta-analysis of mean weight gains.

Results. We found 11 primary studies reporting the effects of APs on body weight or body mass index (BMI) in AP-naive patients. The mean body weight and BMI gains in AP-naive patients were highly significant from the first weeks of treatment. When we limited the analysis to studies conducted on patients hospitalized and without any adjunctive treatment potentially affecting weight, the resultant sample showed less heterogeneity and confirmed the final picture of weight gain at around 3.8 kg and 1.2 points BMI.

Conclusions. Weight gain associated with AP therapy in AP-naive patients occurs rapidly in the first few weeks and continues during the following months. Clinicians should be aware of the high probability of causing weight gain in AP-naive patients and should strictly monitor such patients.

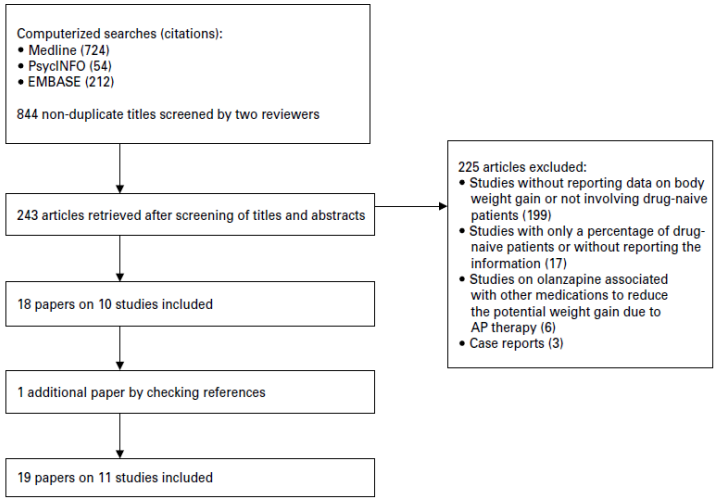


Fig. 1. Selection of studies.

Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research 157 (2008) 269–271
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Brief report

Metabolic side effects of second generation antipsychotic agents in antipsychotic-naïve patients: One-month prospective evaluation

Ilaria Tarricone, Alessandro Serretti *, Beatrice Ferrari Gozzi, Laura Mandelli, Daniela Grieco, Lorenzo Mellini, Stefano Biagini, Beatrice Berti, Domenico Berardi

Institute of Psychiatry "P. Ottonello", University of Bologna, Italy

Received 16 August 2006; received in revised form 10 April 2007; accepted 10 July 2007

Abstract

The present study investigated the effects of second generation antipsychotics (SGA) on the metabolism of 15 antipsychotic-naïve outpatients. Evaluations were performed at baseline and after 1 month of treatment. A significant increase in mean body mass index (BMI) and mean waist circumference was observed. These results suggest the importance of monitoring patients from the first few weeks of antipsychotic treatment.

Keywords: Antipsychotic; Drug naïve; Schizophrenia; Metabolism

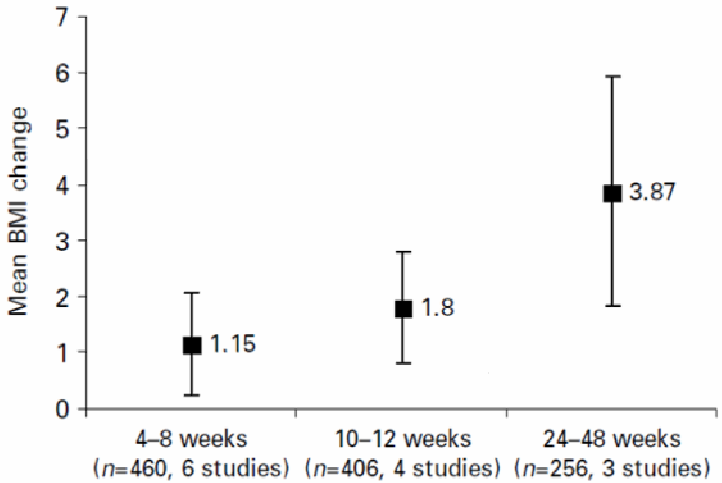


Fig. 3. Body mass index (BMI) mean change at three different follow-up times.

Review article

First- *v.* second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis

M. Smith, D. Hopkins, R. C. Peveler, R. I. G. Holt, M. Woodward and K. Ismail

BJPsych | The British Journal of Psychiatry (2008) 192, 406–411. doi: 10.1192/bjp.bp.107.037184

Methods

Criteria for selecting studies

Abstracts were considered eligible for full manuscript data extraction if they fulfilled the following criteria:

(a) the design was a cross-sectional, case–control, cohort or controlled trial

(b) the study population included children or adults with schizophrenia or related psychotic disorders

(c) second-generation antipsychotics (defined in this study as clozapine, olanzapine, risperidone and quetiapine) were being compared with first-generation antipsychotics (listed in the *British National Formulary* (BNF))[13]

(d) measurement of diabetes as a primary or secondary outcome was included.

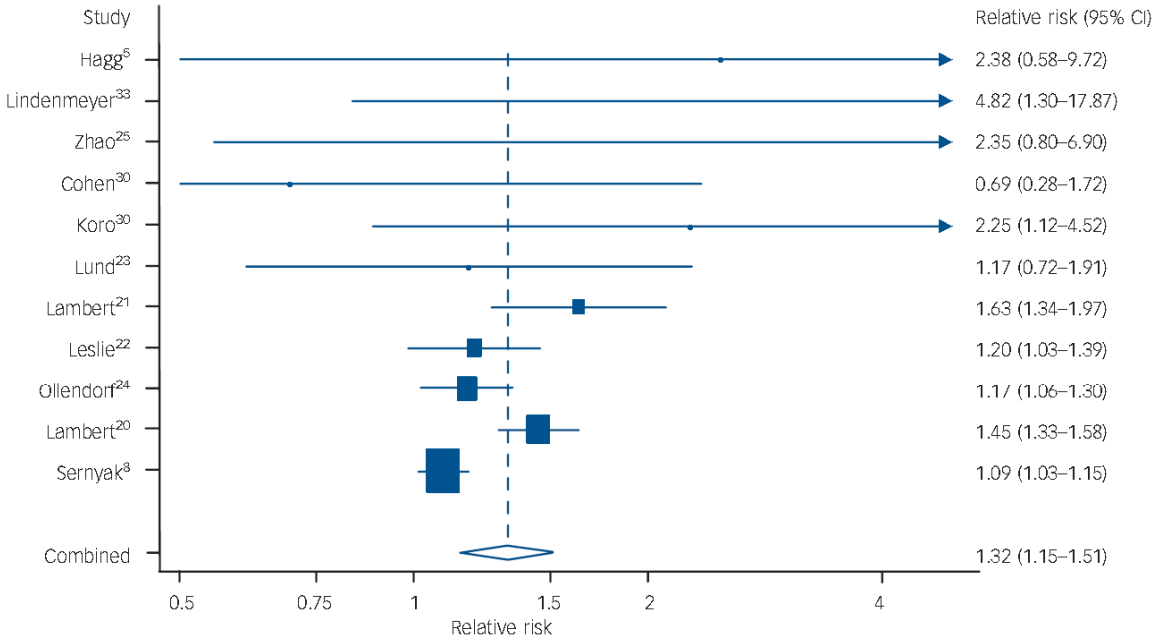


Fig. 2 Forest plot of relative risks and 95% CIs for diabetes in patients on first-generation antipsychotics compared with second-generation antipsychotics.

Estimates are at the centre of the boxes, which are drawn in proportion to the standard errors; lines show 95% CIs. Arrows denote censoring. The diamond shows the combined (pooled) estimate at its centre; its horizontal points lie at the 95% confidence limits for the combined estimate.

BJPsych | The British Journal of Psychiatry (2010) 197, 266–271. doi: 10.1192/bjp.bp.109.076935

Treatment with antipsychotics and the risk of diabetes in clinical practice

Lars Vedel Kessing, Anders Frøkjær Thomsen, Ulla Brasch Mogensen and Per Kragh Andersen

Background
Treatment with antipsychotics seems to increase the risk of developing diabetes but the association is poorly characterised in clinical practice.

Aims
To investigate and characterise the incidence of diabetes for people treated with antipsychotic medication in clinical practice.

Method
The study used the linkage of registers of all prescribed antipsychotics, antidiabetics and diagnoses of diabetes in Denmark during a period from 1996 to 2005 and identified all people treated with antipsychotics in Denmark and a random sample of about 30% of the total Danish population.

Results
In total, 345 937 patients who purchased antipsychotics and 1 426 488 unexposed individuals were included in the study. Among the total population, 50 379 individuals subsequently developed incident diabetes. Compared with unexposed individuals, treatment with first- (rate ratio, RR = 1.53, 95% CI 1.49–1.56) as well as second-generation (RR = 1.32, 95% CI 1.22–1.42) antipsychotics was associated with increased risk of subsequent incident diabetes. The rate of incident diabetes varied substantially between individual second-generation antipsychotic drugs (olanzapine, risperidone clozapine compared with unexposed individuals: low to moderate rate ratio between 1.17 and 1.57; ziprasidone and sertindol: two or more times increased rate ratio; amisulpride, quetiapine and aripiprazole: no significantly increased rate ratio). For both first- and second-generation antipsychotics, the incidence of diabetes increased with the number of prescriptions. Additionally, the incidence of diabetes increased with the number of combined antipsychotic drugs.

Conclusions
In clinical practice, treatment with first- and second-generation antipsychotics is associated with an increased risk of developing incident diabetes with large differences between individual drugs. The risk increases with the duration of treatment and with polypharmacy of antipsychotic drugs.

Declaration of interest
L.V.K. has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth, Servier and Janssen-Cilag.

Table 2 Rate of diabetes related to number of prescriptions for antipsychotics (reference: no prescriptions)[a]

Prescriptions, *n*	Rate ratio (95% CI) First-generation antipsychotics	Rate ratio (95% CI) Second-generation antipsychotics
0	1	1
1–2	1.33 (1.29–1.38)	0.98 (0.84–1.14)
3–4	1.46 (1.38–1.55)	1.61 (1.30–2.00)
5–9	1.53 (1.45–1.62)	1.47 (1.23–1.76)
10–14	1.54 (1.44–1.66)	1.09 (0.83–1.43)
15–19	1.59 (1.46–1.73)	1.49 (1.12–1.99)
20–24	1.79 (1.63–1.97)	1.30 (0.90–1.87)
25–29	1.85 (1.67–2.06)	1.90 (1.32–2.73)
30–34	2.01 (1.80–2.25)	1.74 (1.11–2.73)
35–39	1.93 (1.70–2.19)	0.63 (0.26–1.50)
⩾40	2.04 (1.92–2.16)	1.81 (1.36–2.42)

a. Adjusted for gender, age, calendar period and use of lithium or anticonvulsants.

Table 4 The rate ratios of incident diabetes in relation to the number of different antipsychotic drugs as modelled in the Poisson regression (reference: no prescriptions of antipsychotics)

Antipsychotic drugs compared with reference, *n*	RR ratio (95% CI)
1 antipsychotic *v.* 0	1.48 (1.44–1.51)
2 antipsychotics *v.* 0	1.68 (1.61–1.76)
3 antipsychotics *v.* 0	1.96 (1.82–2.10)
4 antipsychotics *v.* 0	2.38 (2.13–2.65)
5 or more antipsychotics *v.* 0	3.41 (3.03–3.83)

RR, rate ratio.

Table 3 Rate of diabetes related to different antipsychotics (reference: no prescriptions)[a]

Antipsychotic	*n*	Age at first prescription Years: median (25–75%)	Female gender, %	Antipsychotic drug-naive RR (95% CI)	Antipsychotic combined RR (95% CI)
Zuclopenthixol	57 065	65.0 (41.9–82.3)	59.1	**1.40 (1.30–1.50)**	**1.40 (1.33–1.47)**
Perphenazine	21 473	50.0 (36.4–68.2)	56.5	**1.60 (1.45–1.77)**	**1.57 (1.48–1.67)**
Haloperidol	27 872	72.2 (54.6–82.3)	56.6	**1.32 (1.17–1.49)**	**1.17 (1.08–1.26)**
Clozapine	6014	41.1 (30.1–58.7)	43.5	1.29 (0.98–1.70)	**1.45 (1.28–1.64)**
Olanzapine	42 408	46.7 (32.3–69.5)	52.3	**1.35 (1.18–1.54)**	**1.29 (1.20–1.37)**
Risperidone	44 110	54.8 (33.0–78.5)	57.1	**1.24 (1.09–1.40)**	**1.23 (1.15–1.32)**
Ziprasidone	5950	32.7 (24.1–43.3)	60.4	**3.09 (1.54–6.17)**	**1.94 (1.62–2.31)**
Sertindole	371	34.1 (27.2–42.6)	53.1	**9.53 (1.34–67.63)**	**1.94 (1.32–2.84)**
Amisulpride	882	33.4 (24.9–43.5)	47.7	1.72 (0.24–12.23)	1.42 (0.88–2.30)
Quetiapine	12 402	42.3 (28.3–68.0)	57.9	0.71 (0.43–1.18)	1.15 (0.99–1.34)
Aripiprazole	4523	31.3 (23.3–41.5)	51.3	1.99 (0.50–7.97)	1.16 (0.83–1.62)

RR, rate ratio.
a. Adjusted for gender, age, calendar period and use of lithium or anticonvulsants. Results in bold are statistically significant.

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Original article

Type-2 diabetes mellitus in schizophrenia: Increased prevalence and major risk factor of excess mortality in a naturalistic 7-year follow-up

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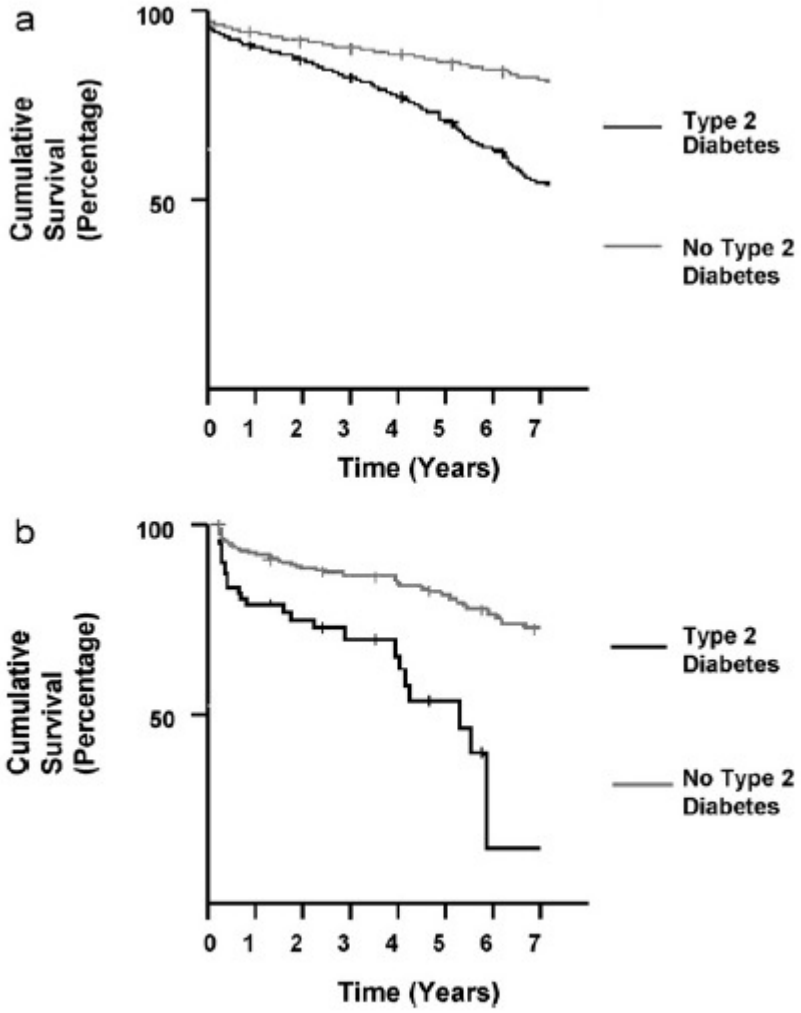

Fig. 1. A. Kaplan-Meier curves showing 7-year mortality curves for control patients with and without Type 2 Diabetes Mellitus. B. Kaplan-Meier curves showing 7-year mortality curves for Schizophrenia patients with and without Type 2 Diabetes Mellitus.

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Diabetes is associated with lower global cognitive function in schizophrenia

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ABSTRACT

Background: Co-morbidity of schizophrenia (SZ) and metabolic problems such as diabetes mellitus (DM) has been suggested by many studies. Nonetheless, it is still debated whether DM affects cognitive dysfunction associated with SZ and how much treatment for DM is beneficial for cognitive functions in SZ. We addressed these questions by re-assessing the cognitive dataset from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study.

Methods: We identified 1289 SZ patients in which scores for several cognitive domains of verbal memory, vigilance, processing speed, reasoning, and working memory together with the composite score and metabolic characteristics (body mass index, dyslipidemia, hypertension, and DM) were available at baseline of the trial. We performed multiple linear regression analyses to assess the impact of DM on cognitive performance of SZ patients, controlling for a number of other confounding factors including obesity, hypertension, and dyslipidemia. We also conducted analyses of covariance to compare cognitive performance among SZ patients without DM and diabetic SZ sub-groups based on anti-diabetic drugs they were receiving at baseline of the trial.

Results: Co-morbid DM with SZ predicted worse overall cognitive performance and lower scores for three cognitive domains (vigilance, processing speed, and reasoning), but none of the other metabolic factors (i.e., obesity, hypertension and dyslipidemia) correlated with cognitive function in SZ. Furthermore, SZ patients with untreated DM showed poorer overall cognitive performance and a significantly lower score in the domain of vigilance compared with SZ patients without DM.

Conclusion: Our data suggest that DM negatively affects the overall cognitive function of SZ patients.

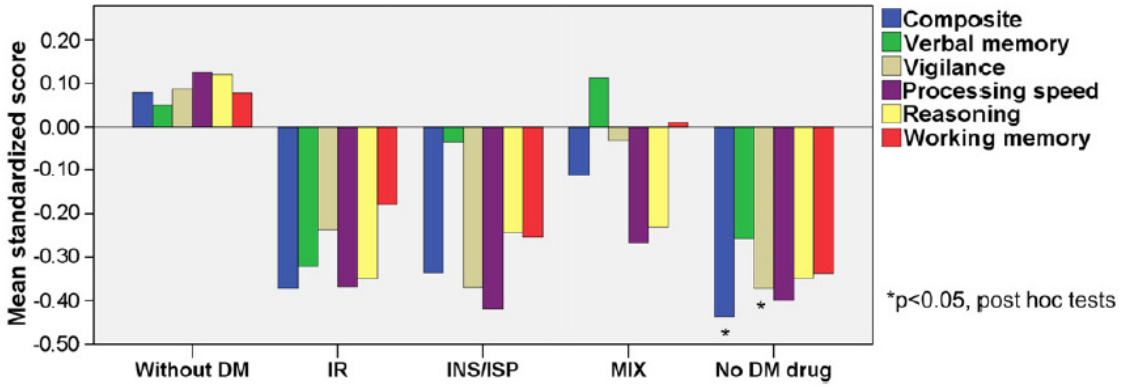

Fig. 1. Comparison of mean standardized scores of neurocognitive composite and five neurocognitive domains (verbal memory, vigilance, processing speed, reasoning and working memory) among schizophrenia patients without diabetes and diabetic schizophrenia patients divided based on receiving anti-diabetic drugs. Positive value indicates better cognitive performance.DM, diabetes mellitus; IR, insulin resistance treatment agents; INS, insulin; ISP, insulin secretion promoter; MIX, receiving both IR and INS/ISP. *p<0.05, results of post hoc tests compared with schizophrenia patients without diabetes.

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

American Diabetes Association
American Psychiatric Association
American Association of Clinical Endocrinologists
North American Association for the Study of Obesity

Weight gain and changes in body composition may account for many of the purported metabolic complications associated with SGA therapy, e.g., insulin resistance, pre-diabetes, diabetes, and dyslipidemia. A possible direct effect of SGAs on β-cell function and insulin action in liver and muscle tissue could also be involved, as discussed below.

Effectiveness of Medications Used to Attenuate Antipsychotic-Related Weight Gain and Metabolic Abnormalities: A Systematic Review and Meta-Analysis

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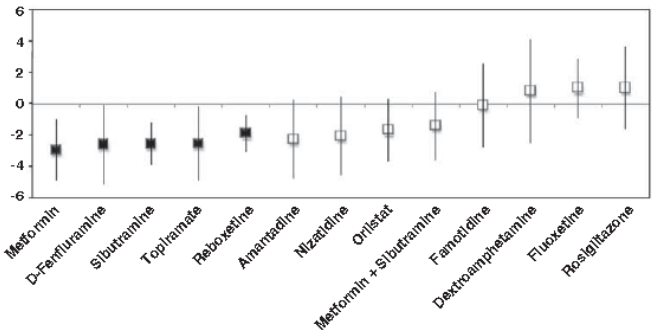

Figure 3 WMD with 95% confidence interval of weight change in kilograms between pharmacologic treatment and placebo. Shaded boxes indicate agents that separated from placebo.

Although metformin outperformed other agents that have been studied against placebo, the current evidence is too limited to support its regular clinical use as an adjunctive medication. Data regarding the metformin related, rare, but potentially fatal side effect of lactic acidosis, particularly in elderly and those with compromised renal function (Chang *et al*, 2002), and its new-found association with the accumulation of beta-amyloid, a factor in the pathogenesis of Alzheimer's disease (Chen *et al*, 2009), alter the risk–benefit ratio in the elderly. However, the results do support further investigation of the risks and benefits of metformin in large, well-controlled trials in comparison with lower risk interventions such as switching to an antipsychotic medication with a lesser cardio metabolic burden, healthy lifestyle interventions and nutritional counseling.

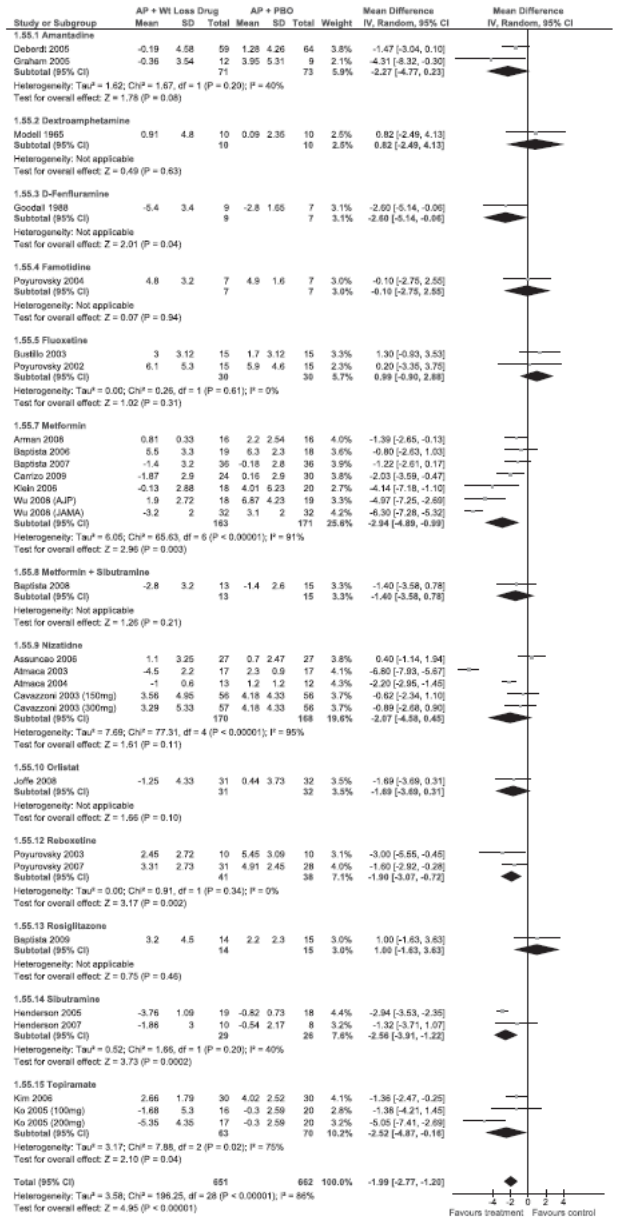

Figure 2 Differences in weight change: forest plot comparing the summarized results and effect sizes (with 95% CIs) for patients on a weight loss medication and those on placebo.

Article

A Randomized Trial Examining the Effectiveness of Switching From Olanzapine, Quetiapine, or Risperidone to Aripiprazole to Reduce Metabolic Risk: Comparison of Antipsychotics for Metabolic Problems (CAMP)

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Jeffrey A. Lieberman, M.D.

for the Schizophrenia Trials Network

Objective: The authors conducted a multisite randomized controlled trial examining the strategy of switching from olanzapine, quetiapine, or risperidone to aripiprazole to ameliorate metabolic risk factors for cardiovascular disease.

Method: Patients with schizophrenia or schizoaffective disorder with a body mass index ≥27 and non-high-density lipoprotein (non-HDL) cholesterol ≥130 mg/dl who were on a stable treatment dosage of olanzapine, quetiapine, or risperidone were randomly assigned to switch to aripiprazole (N=109) for 24 weeks or stay on their current medication (N=106). All participants were enrolled in a behaviorally oriented diet and exercise program. Clinical raters were blinded to treatment assignment. The primary and key secondary outcomes were change in non-HDL cholesterol and efficacy failure, respectively.

Results: The prespecified primary analysis included 89 switchers and 98 stayers who had at least one postbaseline non-HDL cholesterol measurement. The least squares mean estimates of non-HDL cholesterol decreased more for the switch group than for the stay group (–20.2 mg/dl and –10.8 mg/dl, respectively). Switching was associated with larger weight reductions (least squares mean=2.9 kg) and a net reduction of serum triglycerides of 32.7 mg/dl. Twenty-two switchers (20.6%) and 18 stayers (17.0%) experienced protocol-defined efficacy failure. Forty-seven switchers (43.9%) and 26 stayers (24.5%) discontinued the assigned antipsychotic medication before 24 weeks.

Conclusion: Switching to aripiprazole led to improvement of non-HDL cholesterol levels and other metabolic parameters. Rates of efficacy failure were similar between groups, but switching to aripiprazole was associated with a higher rate of treatment discontinuation. In the context of close clinical monitoring, switching from an antipsychotic with high metabolic risk to one with lower risk to improve metabolic parameters is an effective strategy.

(Am J Psychiatry 2011; 168:947–956)

ORIGINAL ARTICLE

A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness

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ABSTRACT

BACKGROUND

Overweight and obesity are epidemic among persons with serious mental illness, yet weight-loss trials systematically exclude this vulnerable population. Lifestyle interventions require adaptation in this group because psychiatric symptoms and cognitive impairment are highly prevalent. Our objective was to determine the effectiveness of an 18-month tailored behavioral weight-loss intervention in adults with serious mental illness.

METHODS

We recruited overweight or obese adults from 10 community psychiatric rehabilitation outpatient programs and randomly assigned them to an intervention or a control group. Participants in the intervention group received tailored group and individual weight-management sessions and group exercise sessions. Weight change was assessed at 6, 12, and 18 months.

RESULTS

Of 291 participants who underwent randomization, 58.1% had schizophrenia or a schizoaffective disorder, 22.0% had bipolar disorder, and 12.0% had major depression. At baseline, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 36.3, and the mean weight was 102.7 kg (225.9 lb). Data on weight at 18 months were obtained from 279 participants. Weight loss in the intervention group increased progressively over the 18-month study period and differed significantly from the control group at each follow-up visit. At 18 months, the mean between-group difference in weight (change in intervention group minus change in control group) was −3.2 kg (−7.0 lb, P=0.002); 37.8% of the participants in the intervention group lost 5% or more of their initial weight, as compared with 22.7% of those in the control group (P=0.009). There were no significant between-group differences in adverse events.

CONCLUSIONS

A behavioral weight-loss intervention significantly reduced weight over a period of 18 months in overweight and obese adults with serious mental illness. Given the epidemic of obesity and weight-related disease among persons with serious mental illness, our findings support implementation of targeted behavioral weight-loss interventions in this high-risk population. (Funded by the National Institute of Mental Health; ACHIEVE ClinicalTrials.gov number, NCT00902694.)

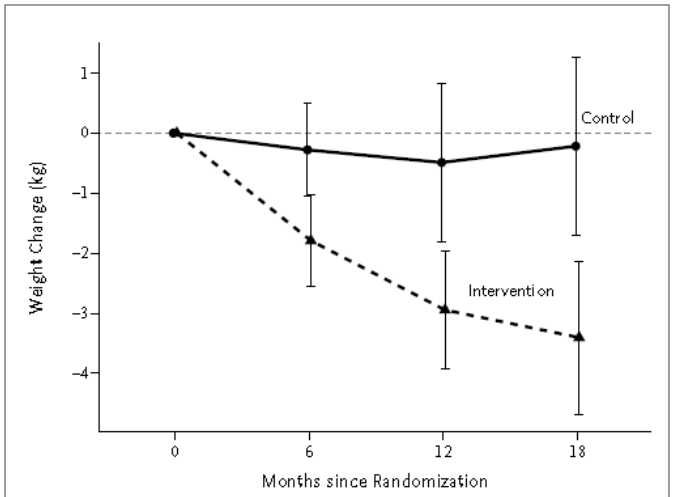

Figure 2. Mean Weight Change, According to Study Group.

The model-based estimates of the mean difference in changes in weight (the change in the intervention group minus the change in the control group) between the two groups at 6, 12, and 18 months were −1.5 kg (95% CI, −2.6 to −0.4; P=0.007), −2.5 kg (95% CI, −4.1 to −0.8; P=0.004), and −3.2 kg (95% CI, −5.1 to −1.2; P=0.002), respectively. To convert values for weight to pounds, multiply by 2.2.

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Guida all'uso dei farmaci antipsicotici per il trattamento della schizofrenia

2007 approvato Commissione Provinciale

La terapia antipsicotica come parte integrante di un programma di cura che comprende interventi rivolti ai bisogni clinici, emotivi e sociali dell'individuo

Sono da evitare le associazioni tra antipsicotici

E' richiesto il monitoraggio degli effetti collaterali metabolici e cardio-circolatori; la gestione della problematica internistica andrà concordata con il MMG.

In regime ambulatoriale dovrebbe essere impiegata la dose minima efficace di un antipsicotico

Gli AP non dovrebbero essere usati come sedativi, a causa dei pericolosi effetti collaterali

Nei pazienti che presentano importanti effetti collaterali metabolici da SGA, o che sono ad alto rischio di svilupparli, è opportuno l'impiego di FGA, qualora questi siano tollerati sul piano degli effetti extrapiramidali e cardiologici ed alle dosi efficaci più basse possibili