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ORIGINAL ARTICLE

Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices

A. J. Mitchell[1,2]*, V. Delaffon[1], D. Vancampfort[3,4], C. U. Correll[5,6] and M. De Hert[3]

[1] *Psycho-oncology, Leicester General Hospital, Leicestershire Partnership Trust, Leicester, UK*
[2] *Department of Cancer Studies and Molecular Medicine, Leicester Royal Infirmary, University of Leicester, UK*
[3] *UPC KUL campus Kortenberg, Belgium*
[4] *Department of Rehabilitation Sciences, Faculty of Kinesiology and Rehabilitation Sciences, Catholic University Leuven, Heverlee, Belgium*
[5] *The Zucker Hillside Hospital, Glen Oaks, New York, USA*
[6] *Albert Einstein College of Medicine, Bronx, New York, USA*

Background. Despite increased cardiometabolic risk in individuals with mental illness taking antipsychotic medication, metabolic screening practices are often incomplete or inconsistent.

Method. We undertook a systematic search and a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) meta-analysis of studies examining routine metabolic screening practices in those taking antipsychotics both for patients in psychiatric care before and following implementation of monitoring guidelines.

Results. We identified 48 studies ($n=290\,534$) conducted between 2000 and 2011 in five countries; 25 studies examined predominantly schizophrenia-spectrum disorder populations; 39 studies ($n=218\,940$) examined routine monitoring prior to explicit guidelines; and nine studies ($n=71\,594$) reported post-guideline monitoring. Across 39 studies, routine baseline screening was generally low and above 50% only for blood pressure [69.8%, 95% confidence interval (CI) 50.9–85.8] and triglycerides (59.9%, 95% CI 36.6–81.1). Cholesterol was measured in 41.5% (95% CI 18.0–67.3), glucose in 44.3% (95% CI 36.3–52.4) and weight in 47.9% (95% CI 32.4–63.7). Lipids and glycosylated haemoglobin (HbA1c) were monitored in less than 25%. Rates were similar for schizophrenia patients, in US and UK studies, for in-patients and out-patients. Monitoring was non-significantly higher in case-record *versus* database studies and in fasting samples. Following local/national guideline implementation, monitoring improved for weight (75.9%, CI 37.3–98.7), blood pressure (75.2%, 95% CI 45.6–95.5), glucose (56.1%, 95% CI 43.4–68.3) and lipids (28.9%, 95% CI 20.3–38.4). Direct head-to-head pre–post-guideline comparison showed a modest but significant (15.4%) increase in glucose testing ($p=0.0045$).

Conclusions. In routine clinical practice, metabolic monitoring is concerningly low in people prescribed antipsychotic medication. Although guidelines can increase monitoring, most patients still do not receive adequate testing.

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Key words: Bipolar disorder, cardiovascular risk, diabetes, dyslipidaemia, guidelines, metabolic syndrome, monitoring, post-intervention, schizophrenia, screening.

Introduction

Physical health problems and specifically metabolic and cardiovascular co-morbidity are recognized as being increasingly important in a range of severe mental illnesses (McIntyre *et al*. 2005; Mitchell & Malone, 2006; Leucht *et al*. 2007; Fleischhacker *et al*. 2008; Bresee *et al*. 2010*a*; De Hert *et al*. 2011). This increased risk is reflected by a high rate of premature mortality in people with mental disorders (Colton & Manderscheid, 2006; Saha *et al*. 2007; Mitchell, 2009; Weinmann *et al*. 2009). Of these populations, people with schizophrenia taking antipsychotic medication often have multiple related cardiovascular and metabolic risk factors, and hence represent a vulnerable group for whom more frequent metabolic monitoring and medical care are indicated (De Hert *et al*. 2008, 2011; Bell *et al*. 2009; Bresee *et al*. 2010*a*). Two large studies of psychiatric in-patients suggest that there is

* Address for correspondence: A. J. Mitchell, Consultant in Psycho-oncology, Leicester General Hospital, Leicester Partnership Trust, Leicester LE5 4PW, UK.
(Email: Alex.Mitchell@leicspart.nhs.uk)

appreciable yield from routine testing of metabolic parameters. Arce-Cordon *et al*. (2007) found that routine testing of 510 newly hospitalized psychiatric patients in Madrid, Spain, yielded 36% with high cholesterol, 23% with hypertriglyceridaemia and 6% with glucose abnormalities. Bernardo *et al*. (2009) found that testing 733 newly admitted in-patients with schizophrenia revealed that 66% had high cholesterol, 17% hypertension, 6% diabetes, 27% hypertriglyceridaemia and 24% obesity. Large-scale studies in psychiatric out-patients or mixed samples confirm these high rates of metabolic abnormalities (Meyer *et al*. 2005; Arango *et al*. 2008; De Hert *et al*. 2008; Shi *et al*. 2009). It is also increasingly recognized that most antipsychotic agents are closely linked with adverse effects on weight, lipids and glucose metabolism and cardiovascular disease (Jin *et al*. 2004; Meyer & Koro, 2004; Newcomer, 2005; Oriot *et al*. 2008; Smith *et al*. 2008; Yood *et al*. 2009; Crossley *et al*. 2010). These effects have recently been summarized using data from 48 randomized controlled antipsychotic drug trials (Rummel-Kluge *et al*. 2010).

In response to these concerns, several management guidelines have been published between 2004 and 2010 (Salokangas *et al*. 2001; Dinan *et al*. 2003; ADA/APA, 2004; Lambert & Chapman, 2004; Marder *et al*. 2004; Melkersson *et al*. 2004; De Nayer *et al*. 2005; Poulin *et al*. 2005; Amati *et al*. 2006; Lefebvre *et al*. 2006; Usher *et al*. 2006; Barnett *et al*. 2007; Cahn *et al*. 2008; Elkis *et al*. 2008; Murasaki *et al*. 2008; Saiz *et al*. 2008; De Hert *et al*. 2009; Saravane *et al*. 2009; Gothefors *et al*. 2011). In the USA, the key guideline is the American Diabetes Association (ADA)/American Psychiatric Association (APA) consensus document (ADA/APA, 2004). This requires regular monitoring of weight, waist circumference, blood pressure, fasting plasma glucose level, and fasting lipid profile. In the UK, two key guidelines are in place: the revised 2009 National Institute for Health and Clinical Excellence (NICE) schizophrenia guidelines and the UK Quality and Outcomes Framework (QOF) for primary care. The QOF in fact provides a financial incentive for general practitioners (GPs) to provide medical screening of patients with schizophrenia, bipolar affective disorder and other psychoses under NM16–19 [focusing on blood pressure, glucose or glycosylated haemoglobin (HbA1c), body mass index (BMI) and cholesterol:high density lipoprotein (HDL) ratio] (www.gpcontract.co.uk/). In addition, there are more general guidelines for hospitalized psychiatric patients, such as the 2002 APA guideline. This more general guideline recommended that routine procedures during psychiatric emergency admissions include 'a comprehensive metabolic panel, complete blood count with differential, thyroid screening panel, urine toxicology, screening test for tertiary syphilis, psychiatric medication levels, and other studies as appropriate, based on the patterns of illness in the patients served' (Allen *et al*. 2002). It is important to note that one important piece of information missing from the guidelines is what level of testing would be appropriate in clinical practice, given that implementation rarely comes close to 100%. It is also far from clear that implementation of these guidelines has been effective. Indeed, most evidence points towards suboptimal medical care in people with psychiatric diagnoses. For example, in the large Canadian Community Health Survey (CCHS cycle 3.1), people with schizophrenia were twice as likely to report unmet healthcare needs (22.0% *v*. 11.8%) compared with people without schizophrenia (Bresee *et al*. 2010*b*). Deficits in the quality of care of individuals with mental ill health have been linked with poor medical outcomes (Mitchell & Lord, 2010). In a comparative review, more than 70% of studies found that patients with psychiatric diagnoses receive inferior quality of care in at least one medical area (Mitchell *et al*. 2009). Thus, despite the acknowledged high risk of cardiometabolic complications in individuals with serious mental illness (SMI) and the availability of clear monitoring guidelines in many countries, there is concern that screening for metabolic abnormalities and monitoring of any such abnormalities is falling short of a reasonable standard of medical care.

Given these concerns, we aimed to systematically examine and quantify the results of studies reporting on routine metabolic screening practices in patients taking antipsychotic medication. We also aimed to examine the impact of the implementation of monitoring guidelines on monitoring practices.

Method

Inclusion and exclusion criteria

We used the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines, a checklist of 27 items that ensure the quality of a systematic review or meta-analysis (Moher *et al*. 2009). The main inclusion criteria were (1) studies examining routine metabolic screening practices for patients under psychiatric care who were prescribed antipsychotics, and (2) studies examining the metabolic screening practices following the implementation of monitoring guidelines. We required studies to assess screening practices using medical databases or medical records (case-notes) and excluded studies using physician self-reported practices. We used the study defined nature and type of mental illness and stratified results into studies reporting on patients with schizophrenia and related psychosis *versus* other diagnoses.

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Search and study selection

We searched Medline/PubMed and EMBASE abstract databases from inception to May 2011. In these databases, the keywords/MeSH terms ('psychi* or mental or bipolar or mood or depression or psychosis or psychotic or schizophr* or severe mental illness or SMI or antipsychotic)[title] were used combined with ('screen* or monitor* or test* or exam*)[title] and (metabolic or glucose or diabetes or lipid)[textword]. In addition, four full text collections were searched: Science Direct, Ingenta Select, Springer-Verlag's LINK and Blackwell-Wiley. In these online databases, the same search terms were used as a full text search and as a citation search. The abstract databases Web of Knowledge and Scopus were searched, using the above terms as a text word search and using key papers in a reverse citation search. Finally, some journals were hand searched[1]† and several experts contacted. Data were extracted using a standard form (available on request) by one author (A.J.M.) and checked by a second author (D.V.). Studies were selected for extraction if they met inclusion criteria and made available proportions of patients who were monitored. Antipsychotic use included current and past use, but we required at least 50% of the sample to be current users. We did not include studies reported in conference abstracts as these usually had insufficient data.

Meta-analysis

We used proportion meta-analysis, pooling proportions tested for each major parameter using STATSDirect 2.7.7 (UK). Heterogeneity was reduced by stratifying, using type of mental illness and country of origin. Despite this, heterogeneity (defined by I^2 >50%) remained moderate to high. Therefore, random effects meta-analysis was used. We required a minimum of three independent studies to justify pooling by test type. Any potential sources of bias were reported. Publication bias was assessed using the Begg–Mazumdar statistic (Begg & Mazumdar, 1994), finding no bias in any area for any calculation (see Table 2).

Guideline concordant standards

As mentioned earlier, in the absence of clear guidance, we defined an *a priori* standard for successful implementation using the following quantitative scores and 'linked qualitative descriptions: <50% monitored as 'inadequate', ⩾50% to <70% as 'suboptimal', ⩾70% to <80% as 'adequate', ⩾80% to <90% as 'good', and ⩾90% as optimal. Analysis of predictors of testing was only possible with reference to plasma glucose because of sample size limitations.

Results

Search results

We identified 48 qualifying studies in 33 publications (Boilson & Hamilton, 2003; Paton *et al*. 2004; Taylor *et al*. 2004; Gul *et al*. 2006; Motsinger *et al*. 2006; Tarrant, 2006; Weissman *et al*. 2006; Kilbourne *et al*. 2007; Mackin *et al*. 2007; Natarajan & D'Silva, 2007; Voruganti *et al*. 2007; Barnes *et al*. 2008; Hsu *et al*. 2008; Jennex & Gardner, 2008; Morrato *et al*. 2008, 2009*a*, *b*, 2010; Crabb *et al*. 2009; Haupt *et al*. 2009; Holt *et al*. 2009; Nguyen *et al*. 2009; Shi *et al*. 2009; Batscha *et al*. 2010; Bobes *et al*. 2010; Copeland *et al*. 2010; Gonzalez *et al*. 2010; Gumber *et al*. 2010; Hetrick *et al*. 2010; Mangurian *et al*. 2010; Organ *et al*. 2010; Khatana *et al*. 2011; Moeller *et al*. 2011). Thirty-nine studies looked at routine or pre-guideline care and nine looked at post-guideline care. In addition, seven studies examined change in screening practices before and after guideline implementation in a comparable sample. Of the 48 included studies, 24 used data from medical notes (chart review), 22 used retrospective data from medical databases, but two had an unclear data source. Twenty-eight studies examined a population with predominantly schizophrenia and related disorders and 12 had mixed psychiatric samples. All studies were conducted between 2000 and 2011 (Table 1).

Routine testing rates (all subgroups)

Thirty-nine studies involving 218 940 patients in the UK, Canada, Spain, the USA and Australia examined screening practices in routine clinical care without (or before) the influence of enhancements to improve quality of metabolic care. Of all studies on unique samples, 19 examined practices regarding weight monitoring, 14 blood pressure, 31 glucose monitoring, 23 lipids, seven cholesterol, five triglycerides, and eight HbA1c screening. Only eight studies explicitly reported on monitoring in fasting samples.

Meta-analytic rates for each monitoring parameter are shown in Table 2. The highest rate of monitoring was for blood pressure, which was conducted in 69.8% (95% CI 50.9–85.8) of patients routinely. Next most common was monitoring of triglycerides (59.9%, 95% CI 36.6–81.1), followed by weight monitoring (47.9%, 95% CI 32.4–63.67), plasma glucose (44.3%, 95% CI 36.3–52.4) and cholesterol (41.5%, 95% CI 18.0–67.3). General lipid monitoring and HbA1c screening were conducted relatively infrequently

† The notes appears after the main text.

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Table 1. *Methodological overview table of metabolic monitoring studies in patients taking antipsychotics*

	Study year	Sample	Design	Country	Mean age (years)	Gender (% females)	Ethnicity (% non-white)	Diagnosis	Method of data collection	*n*
Pre-guideline										
Boilson & Hamilton (2003)	2001	All in-patient admissions to an acute mental health ward during study period (3 months)	Cross-sectional survey	UK	N.R.	N.R.	N.R.	ICD-10: schizophrenia, schizo-affective/persistent delusional/acute and transient psychotic disorder	Case-note review	44
Paton *et al.* (2004)	2002–2003	In-patients	Cross-sectional survey	UK	38.8	36	49.8	Schizophrenia or schizo-affective disorder (74%), bipolar affective disorder (11%), depression (7.6%), and the remaining other disorders (7.3%)	In-patient prescription charts	606
Taylor *et al.* (2004)	2002–2003	In-patients	Cross-sectional survey	UK	39	32.2	47.2	Schizophrenia and schizo-affective disorder (69.4%), bipolar affective disorder (10.9%), depression (6.1%), personality disorder (2.3%), other (11.3%)	Case-note review	606
Gul *et al.* (2006) baseline	2005–2006	In-patients prescribed clozapine	Retrospective database study with analysis of baseline and 12-month follow-up	UK	N.R. but 45% were between 25 and 40, 48.3% between 40 and 60	13	58	Schizophrenia and related psychoses	Laboratory database	60
Motsinger *et al.* (2006)	2004	In- and out-patients in a community setting	Retrospective laboratory database review	USA	N.R.	N.R.	N.R.	Bipolar disorder (35.6%), schizophrenia (30.0%), schizo- affective disorder (10.0%), and mood and anxiety disorders (24.4%)	Adminstrative database	281
Tarrant (2006)	2004	Community sector-based patients	Cross-sectional survey	UK	N.R.	45	N.R.	ICD-10: (antipsychotic) 74% functional psychosis (F20–29), 21% affective psychosis (F30–39). 1% organic mania (F06.3) and 1% emotionally unstable personality (F60.3)	Psychiatric case-notes, Trust pharmacy records, GP prescribing records, pathology records	55

Natarajan & D'Silva (2006) (baseline)	2003	In-patients in a regional secure unit	Baseline audit	UK	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Weissman *et al*. (2006)	1999–2003	VA sites in New York	Retrospective database study	USA	45.9	6	N.R.	Schizophrenia/schizo-affective disorder	VA administrative database	408
Mackin *et al*. (2007)	2005	Prospective cohort study of community-treated psychiatric patients prescribed an antipsychotic; followed up mean 599 days	Prospective cohort study of community-treated patients to investigate changes in metabolic status and monitoring practices for metabolic and cardiovascular disease. Carried out detailed anthropometric and metabolic assessment at baseline and follow-up	UK	44.2	51	12	Bipolar disorder (35.6%), schizophrenia (30.0%), schizo-affective disorder (10.0%), and mood and anxiety disorders (24.4%)	Case-note review and hospital laboratory results	90
Kilbourne *et al*. (2007)	2004–2006	Population-based study	Based on APA and ADA guidelines, whether patients received recommended lipid and glucose tests for atypical antipsychotics on or within 6 months of antipsychotic prescription	USA	49	14.3	22.8	Bipolar I disorder (74%), bipolar II (2%), bipolar NOS (7%), and schizo-affective disorder – bipolar subtype (17%)	VA administrative database, pharmacy records and laboratory results	252
Voruganti *et al*. (2007)	2005	Cross-sectional survey of a sample of community-dwelling adults (aged ⩾16 years)	Sample identified through the 'snowballing' technique, from five communities differing in sociodemographic characteristics – urban/rural, multicultural/homogeneous	Canada	44.4 (2.67)	37.2	18.2	DSM-IV: schizophrenia or schizo-affective disorder	Case-note review and obtaining corroborating information from the subject's health-care professionals (family physicians, psychiatrists and case managers)	1123
Barnes *et al*. (2008) (baseline)	2005–2006	Community AOT patients	Retrospective audit with 1 year follow-up	UK	16–25 (9%), 26–35 (28.4%), 36–45 (34%), 46–55 (17%), 56–65 (9%), >65 (1.6%)	30.2	32	ICD-10: F20–29 (82%)	Case-note review – baseline audit results	1966

[*continued overleaf*

Table 1 (*cont.*)

	Study year	Sample	Design	Country	Mean age (years)	Gender (% females)	Ethnicity (% non-white)	Diagnosis	Method of data collection	*n*
Hsu *et al.* (2008)	2001–2003	VA health-care system	Veterans on SGAs for 3 months and switched to different SGA for 6 months included in the study, monitoring pre-switch and monitoring post-switch of SGAs	USA	51.6 (10.6)	6.8	45	ICD-9: schizophrenia and schizo-affective disorder	VA database, pharmacy records and laboratory results	1826
Morrato *et al.* (2008)	1998–2003	Medicaid claims data	Retrospective cohort study using Medicaid claims data for California, Oregon, Tennessee and Utah for SGA prescription claims	USA	<19 (12%), 20–29 (13%), 30–39 (19%), 40–49 (20%), 50–59 (12%), 60–69 (1.6%), >70 (1.7%)	50.2	41	Antipsychotic prescription for SGA; aripiprazole, clozapine, olanzapine, quetiapine risperidone or ziprasidone, includes 79.7% with schizophrenia	Medicaid claims from Oregon, California, Tennessee and Utah	55 436
Jennex & Gardner (2008)	2002–2005	Mental health clinics with at least two visits yearly and a minimum follow-up period of 6 months	Retrospective chart review of mental health clinic out-patients taking antipsychotics long-term (3 months) and HIV out-patients prescribed highly active antiretroviral therapy (control subjects)	Canada	44.9 (12.2)	40	N.R.	Patients taking antipsychotics includes schizophrenia (49.5%), schizo-affective disorder (17%), schizophreniform disorder (2%), psychotic disorder NOS (10%) or bipolar disorder (21%)	Case-note review (out-patient charts)	99
Holt *et al.* (2009)	2006	In-patients	Records of 50 consecutive in-patients examined for evidence of monitoring for metabolic syndrome	UK	38.6 (1.1)	N.R.	0	Schizophrenia (66%), affective disorders (25%), drug-induced psychosis (7%), personality disorder (2%)	Case-note review	50
Holt *et al.* (2009)	2006	Out-patients	Records of 50 consecutive out-patients examined for evidence of monitoring for metabolic syndrome	UK	38.6 (1.1)	N.R.	0	Schizophrenia (66%), affective disorders (25%), drug-induced psychosis (7%), personality disorder (2%)	Case-note review	50

Shi *et al.* (2009)	2002–2005	Population-based study	Veterans' electronic records were used to identify patients with schizophrenia who received a new episode of SGA treatment. Patients who underwent metabolic monitoring (either blood glucose or lipid testing records) were compared with patients who did not	USA	54.86	6.55	53.9	ICD-9: schizophrenia	Veterans' electronic records	4709
Haupt *et al.* (2009)	2000–2003	National Insurance claims database, patients (<65) initiated on SGA aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone included	Monitoring rates before the ADA guidelines at baseline and at 12-week follow-up	USA	45.8 (24.8)	53	N.R.	Patients taking antipsychotics includes: schizophrenia (4%), bipolar (17%), depressive disorders (26%), none of the above (54%)	Insurance claims data	5787
Morrato *et al.* (2009*a*)	2001–2004	Population-based study	Retrospective cohort study, adults initiating SGA, glucose and lipid tests within 6 months of starting SGA monitored. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Baseline and follow-up	USA	46.6 (17)	58.7	N.R.	Schizophrenia (2.4%), psychosis (5.4%), bipolar affective disorder (14.4%), depressive disorder (33.1%), anxiety disorder (16.2%)	Administrative claims data, pharmacy and laboratory records	7904

[*continued overleaf*

Table 1 (*cont.*)

	Study year	Sample	Design	Country	Mean age (years)	Gender (% females)	Ethnicity (% non-white)	Diagnosis	Method of data collection	*n*
Morrato *et al.* (2009*b*)	2001–2006	Population-based study	Monitoring rates before and after the ADA consensus statement recommending metabolic monitoring for SGA-treated patients	USA	20–29 (13.2%), 30–39 (19.0%), 40–49 (25.2%), 50–59 (20.1%), 60–69 (8.1%), 70–79 (6.4%), 80–88 (7.7%)	59.3	N.R.	ICD-9: schizophrenia (3.4%), affective disorders (49.3%), anxiety disorders (29.2%), alcohol and substance abuse (15.0%), senility (10.4%), other psychoses (9.4%), pre-adult disorders (4.1%), other mental conditions (51.4%)	Administrative claims data from four commercial health insurance plans	18 876
Crabb *et al.* (2009)	2009	Patients accepted by early intervention psychosis	N.R.	UK	N.R.	N.R.	N.R.	N.R.	Case-note review	90
Nguyen *et al.* (2009)	2005	In-patients on acute ward (16–70 years)	Discharge case-notes were reviewed to establish monitoring rates	Australia	36.5 (11.3)	31.2	N.R.	Schizophrenia in-patients	In-patient notes	93
Gonzalez *et al.* (2010) first audit: baseline	2004–2005	Community sector-based patients	Randomly selected patients treated with antipsychotics except clozapine: audit – baseline results	UK	42.43 (13)	40.5	68	Schizophrenia (44.4%), other diagnoses N.R.	Case-note review	126
Copeland *et al.* (2010)	2001–2005	VA mixed sample	Sample without diabetes at baseline; 32% tested for with fasting glucose of HbA1c in 2002, increased to 34% in 2003, 38% in 2004 and 40% in 2005	USA	59.6 (9.4)	3.4	N.R.	Schizophrenia	VA database and pharmacy records and laboratory results	39 226
Morrato *et al.* (2010) pre-warning	2002–2003	Medicaid claims data	Metabolic testing of cohort of patients initiated on SGA compared with cohort on albuterol over three time periods relating to FDA warnings regarding risks with SGAs	USA	6–12 (11.6%), 13–19 (12.5%), 20–29 (13.6%), 30–39 (16.7%), 40–49 (21.9%), 50–59 (16.1%), 60–69 (6%), 70–79 (1%), 80–88 (1%)	52.9	30.7	Patients taking antipsychotics includes: schizophrenia (15.4%), other psychosis (15%), affective disorder (37.8%), anxiety disorder (29.1%), alcohol and substance use (20.5%)	Medicaid claims data, prescription for SGA aripiprazole, olanzapine, quetiapine risperidone or ziprasidone, from Oregon, California and Missouri	57 900

Gumber *et al*. (2010) (baseline)	2006–2007	Metabolic clinic set up to monitor for metabolic side-effects for patients prescribed antipsychotics from a single catchment area. Baseline audit. In-patients on regular antipsychotic medication	Data recorded at the clinic used to carry out baseline audit	UK	40.7	46.2	N.R.	N.R.	Clinical records from metabolic clinic	96
Bobes *et al*. (2010) (baseline)	2007 (January)	Multicentre Spanish out-patients	Baseline audit of monitoring practice in Spain before Spanish consensus guidelines	Spain	39.7	34.1	N.R.	Schizophrenia (ICD-10)	Case-note review	1193
Hetrick *et al*. (2010)	2010	First-episode psychosis clinic	Monitoring which protocols in place	Australia	15–25	N.R.	N.R.	N.R.	Case-note review	108
Batscha *et al*. (2010)	2007–2008	First-episode psychosis started on antipsychotic in-patients	Excludes nine (22.5%) referred to a metabolic monitoring clinic	USA	23.7	27.50	N.R.	Psychosis including 45% schizophrenia	Case-note review	12
Batscha *et al*. (2010)	2007–2008	First-episode psychosis started on antipsychotic out-patients	Excludes nine (22.5%) referred to a metabolic monitoring clinic	USA	23.7	27.50	N.R.	Psychosis including 45% schizophrenia	Case-note review	19
Organ *et al*. (2010)	2009	Mixed mental health provider	N.R.	Australia	N.R.	N.R.	N.R.	N.R. (any)	Case-note review	618
Mangurian *et al*. (2010)	2010	In-patients	Cross-sectional survey	USA	37.6	53.1	0	Schizophrenia (38.8%), bipolar disorder (28.6%), depressive disorder (10.2%), unspecified psychosis (18.4%), adjustment reaction (4.1%)	Review of patients charts	49
Khatana *et al*. (2011)	2011	Mixed VA patients	Retrospective database analysis	USA	55.7 (±12.3)	7.5	N.R.	Bipolar disorder (822), schizophrenia (222) and schizo-affective disorder: 357 of whom 67.4% taking antipsychotics	VA database	1401

[*continued overleaf*

Table 1 (*cont.*)

	Study year	Sample	Design	Country	Mean age (years)	Gender (% females)	Ethnicity (% non-white)	Diagnosis	Method of data collection	*n*
Moeller *et al.* (2011)	2011	Mixed Medicaid patients	Convenience sample of Medicaid patients seen January 2002–December 2003	USA	43.8	48.7	14.7	Schizophrenia by ICD-9	Medicaid database	2204
Post-guideline										
Natarajan & D'Silva (2007) (re-audit)	2006	In-patients in a regional secure unit	Re-audit	UK	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Barnes *et al.* (2008) (re-audit)	2005–2006	Community AOT patients	Retrospective audit with 1 year follow-up	UK	16–25 (9%), 26–35 (28.4%), 36–45 (34%), 46–55 (17%), 56–65 (9%), >65 (1.6%)	30.2	32	ICD-10: F20–29 (82%)	Case-note-based audit – 1 year follow-up audit results	1516
Haupt *et al.* (2009) post-guideline: baseline	2004–2006	National Insurance claims database, patients (<65) initiated on SGA aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone included	Monitoring rates post-ADA guidelines at baseline and at 12-week follow-up	USA	43.1 (24.9)	53	N.R.	Patients taking antipsychotics includes: schizophrenia (4%), bipolar (17%), depressive disorders (26%), none of the above (54%)	Insurance claims data	17 832
Gonzalez *et al.* (2010) re-audit: baseline	2005–2006	Community sector-based patients	Re-audit results following educational intervention and prompts	UK	42.46 (11.86)	45	64	Schizophrenia (50.9%)	Case-note review	106

Morrato *et al*. (2010) post-warning	2004–2005	Medicaid claims data	Metabolic testing of cohort of patients initiated on SGA compared with cohort on albuterol over three time periods relating to FDA warnings regarding risks with SGAs	USA	6–12 (11.6%), 13–19 (12.5%), 20–29 (13.6%), 30–39 (16.7%), 40–49 (21.9%), 50–59 (16.1%), 60–69 (6%), 70–79 (1%), 80–88 (1%)	52.9	30.7	Patients taking antipsychotics includes: schizophrenia (15.4%), other psychosis (15%), affective disorder (37.8%), anxiety disorder (29.1%), alcohol and substance use (20.5%)	Medicaid claims data, prescription for SGA aripiprazole, olanzapine, quetiapine risperidone or ziprasidone, from Oregon, California and Missouri	31 193
Gumber *et al*. (2010) (re-audit)	2007–2009	Metabolic clinic set up to monitor for metabolic side-effects for patients prescribed antipsychotics from a single catchment area. Baseline audit. In-patients on regular antipsychotic medication	Data recorded at the clinic used to carry out baseline audit	UK	38.2	42.7	N.R.	N.R.	Clinical records from metabolic clinic	184
Bobes *et al*. (2010) (re-audit)	2008 (February)	Multicentre Spanish out-patients	Re-audit of monitoring practice in Spain after Spanish consensus guidelines	Spain	39.7	34.1	N.R.	Schizophrenia by ICD-10	Case-note review	1193
Moeller *et al*. (2011)	2011	Mixed medicaid patients	Convenience sample of Medicaid patients seen January 2002–December 2003	USA	42.9	51.4	22	Schizophrenia by ICD-9	Medicaid database	1638

VA, Veterans Administration; AOT, Assertive Outreach Teams; APA, American Psychiatric Association; ADA, American Diabetes Association; SGA, second-generation antipsychotic; NOS, not otherwise specified; FDA, Food and Drug Administration; HbA1c, glycosylated haemoglobin; GP, general practitioner; N.R., not recorded.

Table 2. *Meta-analytic pooled rates of metabolic monitoring before and after guideline implementation*

	Baseline studies		Post-guideline studies		
	Rate of testing	Heterogeneity (I^2 inconsistency) Publication bias (Begg–Mazumdar test)	Rate of testing	Heterogeneity (I^2 inconsistency) Publication bias (Begg–Mazumdar test)	Pre-post pooled change (%)
Weight monitoring	47.9 (32.4–63.67) $n=19$ [inadequate]	99.6 (99.6–99.6) Kendall's $\tau=0.06$, $p=0.73$	75.9 (37.3–98.7) $n=3$ [adequate]	99.7 (99.7–99.7) Kendall's τ Insufficient data	28.0
Blood pressure monitoring	69.8 (50.9–85.8) $n=14$ [suboptimal]	99.7 (99.7–99.7) Kendall's $\tau=-0.1$, $p=0.6$	75.2 (45.6–95.5) $n=3$ [adequate]	99.5 (99.4–99.6) Kendall's τ Insufficient data	5.4
Glucose monitoring	44.3 (36.3–52.4) $n=30$ [inadequate]	99.9 (99.9–99.9) Kendall's $\tau=0.02$, $p=0.9$	56.1 (43.4–68.3) $n=7$ [suboptimal]	99.8 (99.8–99.8 %) Kendall's $\tau=0.2$, $p=0.6$	11.8
Lipid monitoring	22.2 (16.4–28.7) $n=23$ [inadequate]	99.8 (99.8–99.9) Kendall's $\tau=0.1$, $p=0.5$	37.2 (23.7–51.9) $n=7$ [inadequate]	99.8 (99.8–99.8) Kendall's $\tau=0.5$, $p=0.3$	15.0
Cholesterol monitoring	41.5 (18.0–67.3) $n=7$ [inadequate]	99.5 (99.5–99.6) Kendall's $\tau=0.1$, $p=0.8$	Insufficient data	Insufficient data	N.A.
Triglyceride testing	59.9 (36.6–81.1) $n=5$ [suboptimal]	98.9 (98.6–99.1) Kendall's $\tau=-0.2$, $p=0.5$	Insufficient data	Insufficient data	N.A.
HbA1c screening	16.0 (7.5–26.9) $n=10$ [inadequate]	99.5 (99.5–99.6) Kendall's $\tau=0.02$, $p>0.9$	Insufficient data	Insufficient data	N.A.

N.A., Not available.

Rates and heterogeneity given as percentage (95% confidence interval).

Grade of monitoring according to the following: <50% as 'inadequate', ⩾50% as 'suboptimal', ⩾70% monitored as 'adequate', ⩾80% as 'good' and ⩾90% as optimal.

(22.2% and 16.0% respectively) (see Appendices 1–4). Of note, clinicians who were prepared to measure glucose in the fasting state had testing rates of 56.7% compared with 27.9% in those conducting non-fasting screening.

Routine testing rates in schizophrenia and related psychosis

Twenty-five studies ($n=169\,289$) examined monitoring in patients with schizophrenia and related psychosis. The highest rate of monitoring was for blood pressure, which was conducted in 57.9% (95% CI 34.9–79.3) of patients, followed by glucose (40.0%, 95% CI 30.1–50.3) and weight monitoring (38.6%, 95% CI 23.5–54.9). Blood lipids were tested relatively infrequently (10.1%, 95% CI 9.9–10.3) and so was HbA1c (12.1%, 95% CI 5.7–20.4). Cholesterol was measured in 33.3% (95% CI 6.4–68.5) and triglycerides in 49.6% (95% CI 18.2–81.3). None of these monitoring rates were significantly different to samples without schizophrenia.

We also examined whether rates differed at the start of or during the course of prescription with an antipsychotic medication. Prior to treatment, glucose was monitored in 35.3% of cases (95% CI 24.5–46.9) and following initiation of treatment, glucose was monitored in 33.2% of cases (95% CI 16.5–52.5), suggesting no appreciable difference according to phase of treatment.

Correlates of glucose screening rates (*Fig. 1*)

In studies from the USA, 37.3% ($n=16$, 95% CI 27.1–48.1) received plasma glucose testing as part of routine (pre-guideline) care. In the UK, the equivalent proportion was 41.6% ($n=10$, 95% CI 28.8–55.0). Nineteen studies reported on glucose monitoring according to the notations in the medical notes, with a rate of 48.7% (95% CI 37.4–60.1) compared with 33.5%

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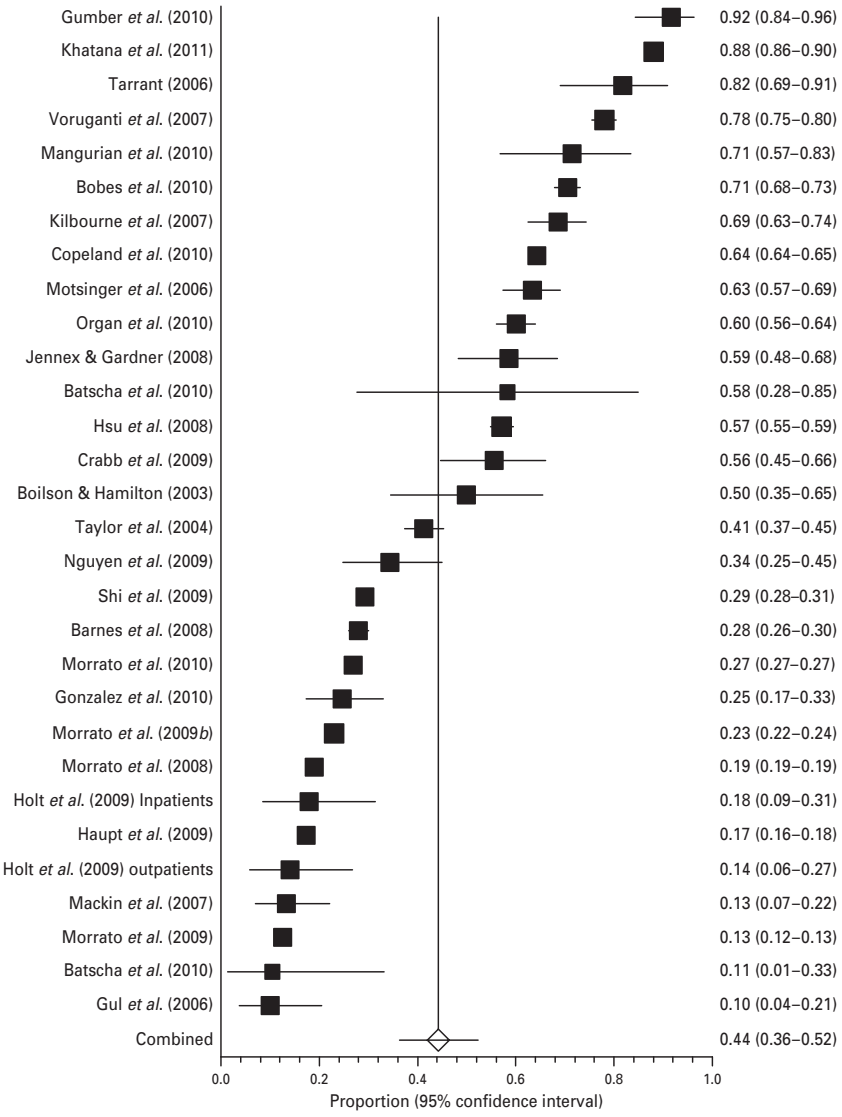

Fig. 1. Routine (pre-guideline) glucose monitoring in patients prescribed antipsychotic medication (random effects).

($n=24$, 95% CI 22.4–45.5) in database studies. For in-patients, 44.0% (95% CI 32.0–56.4) received glucose tests as part of routine care compared with 46.2% (95% CI 26.7–66.4) among out-patients.

Change in monitoring habits following implementation of guidelines

Nine studies (four in the UK, four in the USA and one in Spain; $n=71\,594$) examined monitoring following implementation of guidelines. In these, 75.9% (95% CI 37.3–98.7) received weight monitoring, 75.2% (95% CI 45.6–95.5) had blood pressure monitored, 37.2% (95% CI 23.7–51.9) received lipid monitoring and 56.1% (95% CI 43.4–68.3) glucose testing following guideline implementation. Thus, the most significant improvement seemed to be in weight monitoring, although cautious interpretation is advised because this was an indirect comparison of all studies conducted before and after guideline introduction. Indeed, only a subset of these studies directly compared monitoring rates in the same sample before and after guideline introduction, and from these, only glucose data were sufficient for analysis. Although the overall difference in glucose monitoring was small, seven direct pre–post studies showed a significant 15.4% (95% CI 4.8–25.9) increase [relative risk (RR) 1.47, 95% CI 1.13–1.9] (χ^2 8.1, $p=0.005$) in glucose testing rates following the introduction of guidelines (Fig. 2).

Discussion

Although previous research has documented lower than recommended rates of medical screening procedures in those with a psychiatric diagnosis (Lord *et al*.

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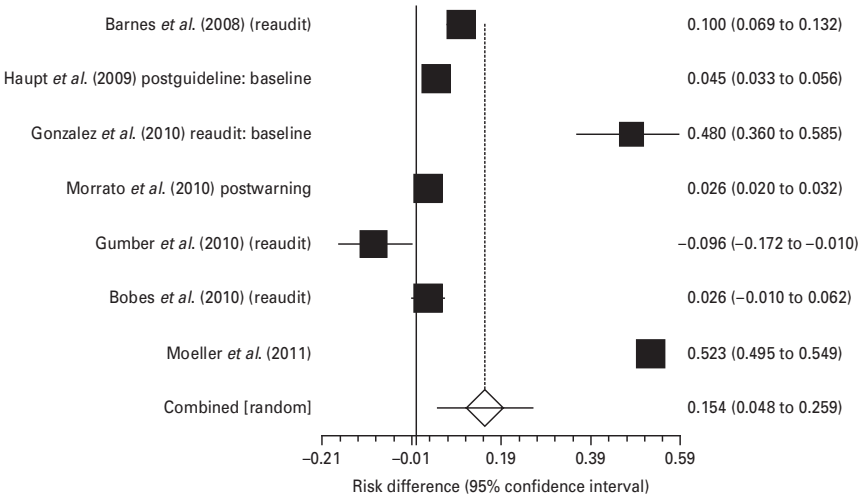

Fig. 2. Pre–post change (risk difference) in glucose monitoring in patients prescribed antipsychotic medication (random effects).

2010), our results show much greater gaps in medical monitoring of the most high-risk patients taking antipsychotic medication. Using data pooled from five countries involving 218 940 patients at baseline and 71 594 post-guideline with mental ill health, we found that metabolic monitoring rates for people with mental illness in receipt of antipsychotic medication are generally low. Indeed, the only parameters where rates of routine monitoring were above 50% were blood pressure and triglycerides. We rated this level of testing *a priori* as 'suboptimal' for these two parameters, as this would still leave at least one-third of patients untested. Most parameters were measured in less than half of patients, namely cholesterol (measured in 41.5%), glucose (measured in 44.3%) and weight (measured in 47.9%), representing 'inadequate' testing according to our nomenclature. This suggests that routine metabolic screening in psychiatric practice is by no means sufficiently robust to detect the high rates of abnormalities found in this population (Cahn *et al*. 2008; De Hert *et al*., in press *a*). We also found that monitoring rates were similar for those with schizophrenia compared to other diagnoses, in US and UK studies and in in-patients and out-patients. Monitoring was essentially the same before initiation of antipsychotic drugs and during longer-term treatment. Yet, following the implementation of local or national guidelines, there was a (modest) statistically significant improvement in only one measure. Based on direct pre–post-guideline studies, there was a small but statistically significant 15.4% increase in glucose testing (RR 1.47, 95% CI 1.13–1.9, χ^2 8.1, $p=0.005$). Although there were also improvements in weight monitoring (change = 28%), blood pressure monitoring (change = 5%) and monitoring lipids (change = 15%), these were not statistically significant. However, it is important to note that, even after guideline implementation, monitoring remained inadequate or suboptimal for most testing procedures and was just adequate only for weight monitoring (75.9% tested) and blood pressure monitoring (75.2% tested).

Future research should focus on the underlying causes for the suboptimal metabolic screening rates, which could provide valuable leads for how to best remediate this problem with high public health relevance. Among the few studies that have addressed this issue, Banta *et al*. (2009) indicated that a lower likelihood of lipid testing [odds ratio (OR) 0.43] was associated with low general functioning [Global Assessment of Functioning (GAF)] scores (Banta *et al*. 2009). Copeland *et al*. (2010) found that predictors of increased glucose testing rates included hypertension (OR 1.36), dyslipidaemia (OR 2.45), medication class count (OR 1.08), younger age (age in decades: OR 0.95) and the presence of an atypical antipsychotic (OR 1.08) (Copeland *et al*. 2010). Shi *et al*. (2009) found that better testing was associated with a concomitant diagnosis of diabetes (OR 2.34), dyslipidaemia (OR 2.44) or hypertension (OR 1.50), or a higher BMI ($\geqslant$28.8) (OR 2.05), substance dependence (OR 1.46) and taking more than one atypical antipsychotic (OR 1.50) (Shi *et al*. 2009). Moeller *et al*. (2011) recently reported that urban older females with schizophrenia, and with known diabetes, had more adequate glucose testing and non-Caucasian females with known diabetes had better lipid testing.

A lack of knowledge about the additive burden of cardiometabolic complications in individuals with mental ill health is a possible explanation for poor monitoring practices, but this does not seem to be supported by the evidence. In 2003, the US Food and Drug Administration (FDA) required that class warnings be added to the labelling of atypical or second-generation antipsychotic (SGA) drugs, describing the increased risk of hyperglycaemia and diabetes, and

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requiring that all drug manufacturers mail health-care professionals about this labelling change (Rosack, 2003). Since then, several studies have examined awareness among mental health professionals of the importance of metabolic factors. Buckley *et al*. (2005) found that US psychiatrists rated metabolic monitoring as a very serious (36%) or serious (61%) concern, but at the same time thought that obtaining waist measurements was 'difficult to obtain/unobtainable' for 42% of respondents. Verdoux *et al*. (2008) asked 54 psychiatrists in France about baseline metabolic screening following a first prescription of an SGA. They reported willingness to measure most parameters in more than half of patients but only 84.6% could access a weighing scale and 44% a tape measure. Suppes *et al*. (2007) surveyed 500 US psychiatrists from the AMA database, and found that 97% were familiar with the metabolic syndrome concept but only 78% of respondents reported monitoring weight, only 69% glucose, 61% lipids, 52% blood pressure and 16% HbA1c. Similar results were found in a parallel European survey (Bauer *et al*. 2008).

It might further be reasoned that a lack of knowledge about existing guidelines and an inconsistency in quality of practice guidelines on screening for metabolic risk could explain, at least in part, the suboptimal monitoring rates. In the study of Suppes *et al*. (2007), only 28% of psychiatrists correctly identified the five National Cholesterol Education Program (NCEP) diagnostic criteria for metabolic syndrome. A recent review of the quality of guidelines for screening and monitoring of cardiometabolic risk in people with schizophrenia concluded that not all guidelines were of sufficient quality to guide clinicians in screening and monitoring practices (De Hert *et al*. 2011). An aspect that should be emphasized is the shared responsibility of screening patients at risk. For example, in an Australian study, 69% of staff members were unsure about who should follow up abnormal cardiometabolic screening results (Organ *et al*. 2010). Numerous recommendations have been made in an attempt to address this problem (Horvitz-Lennon *et al*. 2006; Lambert & Newcomer, 2009; De Hert *et al*., in press*b*). Closer integration of primary care and mental health is needed, but without obscuring the responsibility for testing at key periods, such as upon admission or prior to starting antipsychotic medication. We suggest that testing at these times should be the responsibility of the main mental health professional. However, we acknowledge that many mental health providers do not ask about medical issues or test for them because of lack of consideration of this health care aspect, lack of time or lack of resources directly available to them (Szpakowicz & Herd, 2008). Thus, this basic care may need to be supplemented by physical health clinics (for those under mental health care) (Millar, 2010), metabolic clinics and a system of audit to ensure that testing takes place. Extensive research also suggests that guidelines are difficult to implement (Sheldon *et al*. 2004; Pincus, 2010). Perhaps only one-third of patients receive guideline-concordant, evidence-based care (Cabana *et al*. 1999; Grol, 2001). Frequently reported barriers include lack of resources or time, low organizational support, clinicians' reluctance to change, concerns over the quality of the guidelines and lack of ownership (Cochrane *et al*. 2007; Francke *et al*. 2008; Forsner *et al*. 2010; De Hert *et al*., in press*a*, *b*). In the context of metabolic screening in those with mental health concerns, practice guidelines do not include special recommendations for those patients who receive the least screening and monitoring. Some studies report that the frequency of parameters measured at baseline is lower in women than in men (Buckley *et al*. 2005). As only infrequent separate gender data were available, we were not able to examine this relationship any further. Another factor that might be of relevance when investigating the suboptimal screening and monitoring rates is the setting or context in which patients are treated. For example, primary care visits were positively associated with HbA1c and lipid testing (OR 5.01 and 2.21 respectively) (Lord *et al*. 2010). In a UK primary care setting, those with diabetes and schizophrenia or bipolar disorder had over 90% rates of monitoring of BMI, blood pressure, cholesterol or HbA1c under a newly incentivized QOF system. Moreover, patients seen by a fee-for-service psychiatrist were more likely to have lipid tests (OR 2.35) and eye examinations (OR 2.03). Thus, closer integration of primary care and mental health may, but again, must not obscure responsibility for testing at key treatment periods.

Moreover, effective monitoring of metabolic disturbances is not sufficient on its own, as appropriate treatment is also mandatory. However, patients with psychiatric diagnoses often seem to receive inferior quality of care in several medical areas (Mitchell *et al*. 2009), including metabolic/diabetes care, with six studies having demonstrated inferior care for those with mental illness (Desai *et al*. 2002; Dixon *et al*. 2004; Jones *et al*. 2004; Frayne *et al*. 2005; Krein *et al*. 2006; Kreyenbuhl *et al*. 2006; Weiss *et al*. 2006; Goldberg *et al*. 2007). Effective treatment usually requires effective communication between mental health and primary care services or other specialist medical services (Marder *et al*. 2004; Balf *et al*. 2008). It is particularly concerning that existing evidence suggests that physical co-morbidity is often unrecognized and inadequately treated in those with mental ill health

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(Taylor *et al*. 2005; Bernardo *et al*. 2009; Holt *et al*. 2009; Mitchell, 2009). Unfortunately, diabetes and cardiovascular risk also seem to be considerably under-recognized in this population (McEvoy *et al*. 2005). In the largest controlled study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), approximately one-third of patients met NCEP criteria for metabolic syndrome at baseline, but 88% of patients with dyslipidaemia were untreated, as were 62% with hypertension and 38% with diabetes (Meyer *et al*. 2005; Nasrallah *et al*. 2006; Correll *et al*. 2007). Non-white women were particularly at risk for suboptimal care. In another study, 62% of patients treated with SGA who had elevated low density lipoprotein (LDL) levels did not receive a medical consult or treatment, even though they were in-patients (Correll *et al*. 2007). Bernardo *et al*. (2009) found that among in-patients with schizophrenia, only 60% of those with diabetes, 28% of those with hypertension and 14% of those with dyslipidaemia received active medical treatment. Much of the undertreatment was related to underdetection. For example, 84% of those found to be hypertensive with screening were not recognized as hypertensive on admission.

We acknowledge several limitations in this study. Although we followed the PRISMA principles, we did not have an *a priori* written protocol for this project. Our study is limited by the quality of the included data, which were very limited regarding fasting samples. Studies did not report on the cumulative testing rate over the entire period of care. There was inadequate information on those with established medical and physical co-morbidity. Indeed, only three studies examined monitoring rates in patients with established co-morbidity, such as diabetes. Banta *et al*. (2009) examined medical care given to 482 individuals with diabetes and mental illness in a US Medicaid sample (Lord *et al*. 2010). Only 47.3% received annual HbA1c testing, 56.0% lipid testing and 31.7% eye examinations. Moeller *et al*. (2011) documented about 10% more glucose and lipid complete testing in patients with schizophrenia with *versus* without diabetes following guidelines. In addition, only a few studies looked at monitoring before and after implementation of local guidelines in the same sample. None tested whether clinicians acted appropriately on the findings following testing. We also considered those taking antipsychotics to be relatively homogeneous concerning cardiovascular risk and need for testing. However, several studies examined individuals taking antipsychotics regardless of indication. A study of Medicaid patients found that 64% of adults were receiving an antipsychotic for an off-label indication (Chen *et al*. 2006), and in another large study, 77% of youths receiving an antipsychotic did not have a diagnosis of a psychotic disorder (Staller *et al*. 2005).

Evaluating studies that cover cardiometabolic screening practices over the past 10 years, we conclude that rates of metabolic monitoring are typically suboptimal in those with mental illness prescribed antipsychotic medication, and although improvements are likely after the implementation of guidelines, the majority of patients continue to fail to receive glucose or lipid tests during an episode of care. Closer integration of primary care and mental health may help, but must not obscure responsibility for testing. Basic psychiatric care may need to be supplemented by physical health clinics (for those under mental health care) (Szpakowicz & Herd, 2008), metabolic clinics and a system of audit to ensure that testing and appropriate management of identified abnormalities takes place.

Declaration of Interest

C. U. Correll has been a consultant and/or advisor to or has received honoraria from: Actelion, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, IntraCellular Therapies, Ortho-McNeill/Janssen/J&J, Merck, Otsuka, Pfizer and Sepracor/Sunovion. He has received grant support from the Feinstein Institute for Medical Research, the National Institute of Mental Health (NIMH), and the National Alliance for Research in Schizophrenia and Depression (NARSAD) and Ortho-McNeill/Janssen/J&J. M. De Hert has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory boards of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck JA, Pfizer and Sanofi Aventis.

Notes

[1] *British Journal of Psychiatry*, *Schizophrenia Research*, *Schizophrenia Bulletin*, *Psychological Medicine*, *Acta Psychiatrica Scandinavica*, *American Journal of Psychiatry*, *Archives of General Psychiatry*, *Canadian Journal of Psychiatry*, *Psychiatric Services*, *The Psychiatrist* (previously known as *Psychiatric Bulletin*); all from 2000.

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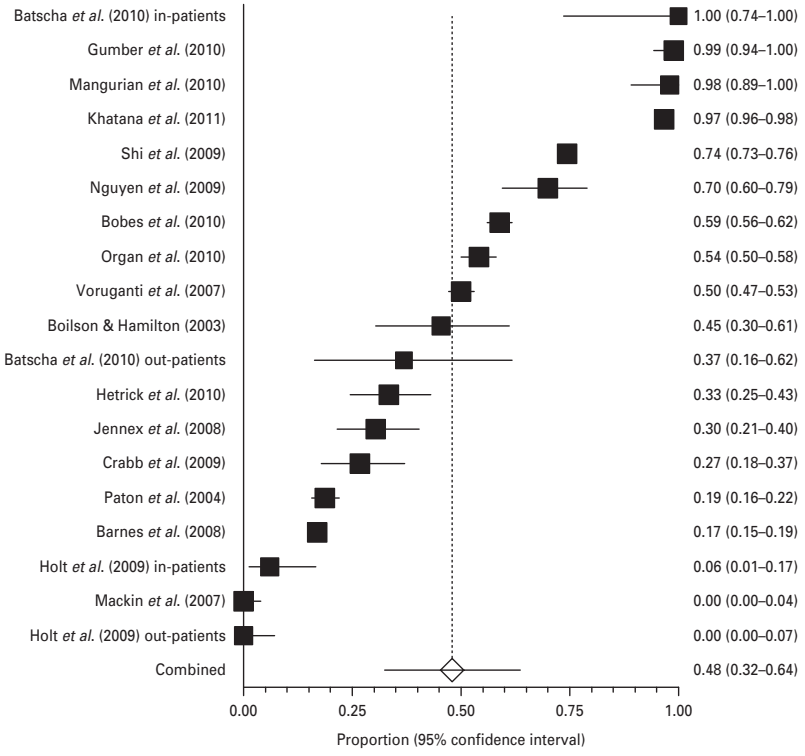
Appendix 1. Routine (pre-guideline) weight monitoring in patients prescribed antipsychotic medication



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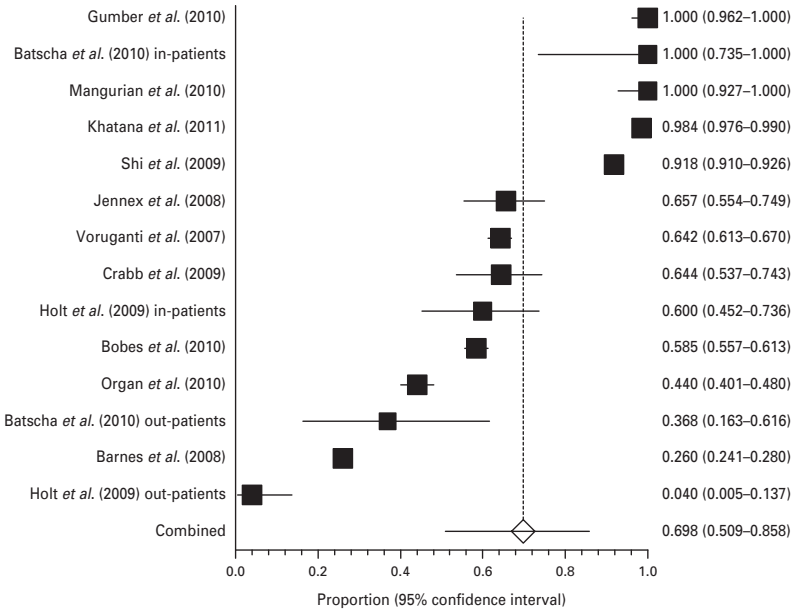
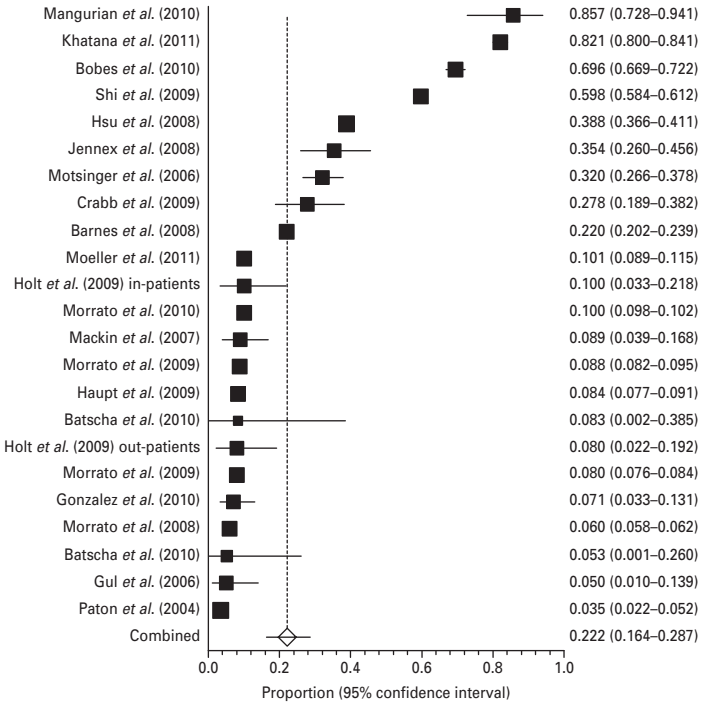
Appendix 2. Routine (pre-guideline) blood pressure monitoring in patients prescribed antipsychotic medication



Appendix 3. Routine (pre-guideline) lipid monitoring in patients prescribed antipsychotic medication



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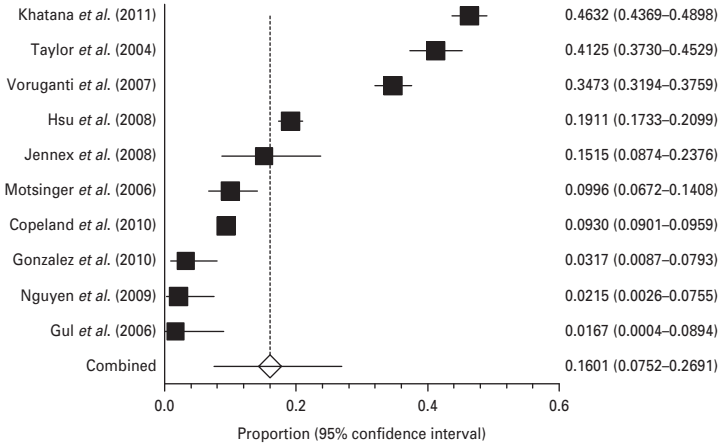
Appendix 4. Routine (pre-guideline) glycosylated haemoglobin (HbA1c) monitoring in patients prescribed antipsychotic medication



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