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Review Article

Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review

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Abstract

Aims To identify real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus.

Methods A literature search was conducted in PubMed and EMBASE in November 2011 to identify studies reporting factors associated with adherence/non-adherence to insulin therapy in adults with Type 1 or Type 2 diabetes.

Results Seventeen studies were identified; six used self-reported measures and 11 used calculated measures of adherence. Most (13/17) were conducted exclusively in the USA. Four categories of factors associated with non-adherence were identified: predictive factors for non-adherence, patient-perceived barriers to adherence, type of delivery device and cost of medication. For predictive factors and patient-perceived barriers, only age, female sex and travelling were associated with non-adherence in more than one study. Fear of injections and embarrassment of injecting in public were also cited as reasons for non-adherence. Conversely, adherence was improved by initiating therapy with, or switching to, a pen device (in four studies), and by changing to an insurance scheme that lowered the financial burden on patients (in two studies).

Conclusions Adherence to insulin therapy is generally poor. Few factors or patient-perceived barriers were consistently identified as predictive for non-adherence, although findings collectively suggest that a more flexible regimen may improve adherence. Switching to a pen device and reducing patient co-payments appear to improve adherence. Further real-world studies are warranted, especially in countries other than the USA, to identify factors associated with non-adherence and enable development of strategies to improve adherence to insulin therapy.

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Introduction

Insulin therapy is essential for patients with Type 1 diabetes mellitus and is ultimately required by over half of patients with Type 2 diabetes mellitus if they are to achieve good glycaemic control [1]. Indeed, guidelines issued by the American Diabetes Association and the National Institute for Health and Clinical Excellence (NICE) state that insulin is the most effective glucose-lowering agent and that insulin therapy is a key component of effective diabetes management over the course of the disease [2–4]. Despite the strong evidence that achieving good glycaemic control helps prevent the development and progression of long-term micro- and macrovascular complications of diabetes [5,6], many patients do not achieve such control. The reported rates of achieving target HbA_{1c} levels are 57–67% in the UK [7,8] and 47–51% in the USA [9,10]. A 5-year retrospective international survey from 18 developing countries across Asia, Eastern Europe and South America reported that only 25% of patients with Type 1 diabetes mellitus and 36% of individuals with Type 2 diabetes mellitus were able to obtain target HbA_{1c} levels [11]. Given the increasing global prevalence of diabetes expected over the next 20–30 years [12,13], early and appropriate initiation of insulin therapy and high levels of adherence to treatment appears to be an effective tool to

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prevent the development and progression of diabetes complications and their negative high socio-economic impact.

Various reasons for reluctance to begin insulin therapy have been identified in patients with Type 2 diabetes, which, combined with prescriptive inertia, can delay treatment initiation. Reasons for reluctance include: fear of hypoglycaemia, weight gain and injection therapy; feelings of personal failure; concerns about being able to cope with the demands of insulin regimens; and perceptions of loss of control over one's life [14,15]. Delayed initiation of insulin therapy will result in poor glycaemic control for many years and development of long-term complications [16]. The situation can be aggravated by poor adherence once insulin therapy has been initiated.

'Adherence' is an umbrella term describing the extent to which a person's behaviour (taking medication, following a diet and/or executing lifestyle changes) corresponds with agreed recommendations from a healthcare provider. The World Health Organization (WHO) estimates that adherence to long-term therapies for chronic illnesses is as low as 50% in the developed world, and is far lower in less developed countries [17]. A systematic review from 2004 reported that adherence rates to insulin varied from 62 to 64% in patients with Type 2 diabetes in developed countries [18]; understanding the reasons for non-adherence to insulin therapy is therefore vital for improving treatment outcomes.

We conducted a systematic literature review to identify real-world factors affecting adherence to insulin therapy in patients with diabetes. By 'real-world' we mean factors affecting adherence encountered by the average patient using insulin outside of a controlled clinical setting such as a clinical trial or a hospital. The study aimed to understand the reasons and choices involved in patients who are prescribed insulin, yet decide not to take it as instructed, despite the overwhelming evidence for the benefits of doing so.

Methods

Adherence was defined as the extent to which patients took their medication as prescribed by their physician. Adherence has two separate components: compliance and persistence [19]. Compliance is the degree to which a patient correctly follows medical advice (administering the right number of injections each day or monitoring blood glucose accurately) and persistence is a measure of the duration for which the patient remains compliant. In this report, the term adherence is used to encompass both compliance and persistence; the terms compliance and persistence are used only when they were specifically written in the primary references. Established measures of adherence include the medication possession ratio (MPR; the total number of days that prescriptions are supplied for in the analysis period divided by the total number of days in the analysis period) and the proportion of days covered [PDC; the number of days during the analysis period for which the patient is covered (i.e. has access to medication) divided by the total number of days in the analysis period] [19]. Many studies use self-administered questionnaires to obtain measures of adherence; the methodology of these questionnaires can vary enormously.

The review included publications assessing adherence to insulin therapy and factors affecting adherence to insulin therapy in patients over 18 years of age with Type 1 or Type 2 diabetes mellitus. Studies not in English or without an abstract were excluded, as were editorials, posters or reviews. Retrospective, prospective, cohort and cross-sectional designs were all included. Randomized controlled trials were excluded because treatment is rigorously controlled, administered and monitored in these studies. Rates of non-adherence will therefore be much lower than in the general population, and reasons for non-adherence will likely be different from those in the general population who self-administer treatment. Studies reporting calculated measures of adherence (e.g. medication possession ratio) and/or patient-reported assessments that examined factors associated with adherence to insulin therapy were included. Only studies reporting adherence to insulin were included; those assessing both insulin and non-insulin therapies were used only if the analysis was performed separately for insulin. Studies involving hospitalized patients were excluded as rates of, and reasons for, adherence are likely to be different in a hospitalized setting, as were studies in patients using insulin pumps that control insulin administration for the patient.

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases on 15 November 2011 using medical subject heading terms for diabetes and medication adherence, as well as terms for interventions for diabetes [e.g. insulin or oral hypoglycaemic agent (OHA)]. The results of the searches were combined and any duplicate references removed. No limit on year of publication was applied. Complete search strings for PubMed and EMBASE are presented in the Supporting Information (Tables S1 and S2, respectively).

References identified from the searches were screened initially according to study title. All accepted references were then screened according to abstract and subsequently on the basis of the full paper to judge inclusion suitability. The bibliographies of all these selected papers were screened for relevant references; no further relevant references were identified. The full screening procedure was performed independently by two separate analysts; screening of references was not blinded. Disagreements between analysts were resolved by consensus.

Data were extracted by one analyst using an extraction table and a second analyst verified all extractions against the original studies. Information extracted included: year of publication, country, type of diabetes, age, gender, ethnicity, duration of follow-up, type of insulin, adherence measure used, definition of adherence, adherence rates, factors

associated with adherence/non-adherence, and statistical tests used to assess the association between factors and adherence.

Study quality was assessed using a shortened version of the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [20], employing only the sections pertaining to selection bias, data collection and withdrawals/dropouts. Other sections were not used as they were tailored towards interventional, comparative study designs and were not deemed relevant to many of the studies included in this review. A global rating scale was therefore not determined, but individual ratings for each section are presented.

The review aimed to identify all relevant published studies describing adherence to insulin therapy and risk factors for poor adherence to insulin therapy, and report all relevant data from these studies. Areas where information appears to be lacking are attributable to incomplete collecting or reporting in the original articles. The limited previous research in this area meant that pre-definition of data for extraction and analysis was not possible. The study aimed to provide a narrative description of the data only. A meta-analysis was not planned, although it was intended to assess whether conducting a meta-analysis on identified data may be feasible.

Results

Search results

The searches returned 3769 articles after duplicates had been removed, of which 3396 were excluded at the title screen (Fig. 1). At the abstract screen, 276 references were excluded; the main reasons for exclusion were that references were not relevant, the investigation studied adherence only to oral hypoglycaemic agents or assessed the effects of varying adherence on factors such as metabolic control, interventions introduced specifically to improve adherence or adherence to diet/lifestyle rather than medication. Full papers were retrieved for the remaining 97 references and 16 of these were judged to meet the criteria for inclusion in the review. The main reason for exclusion at the full-paper screen was not reporting predictors of adherence for insulin alone (i.e. adherence data were not specific for insulin). A further study

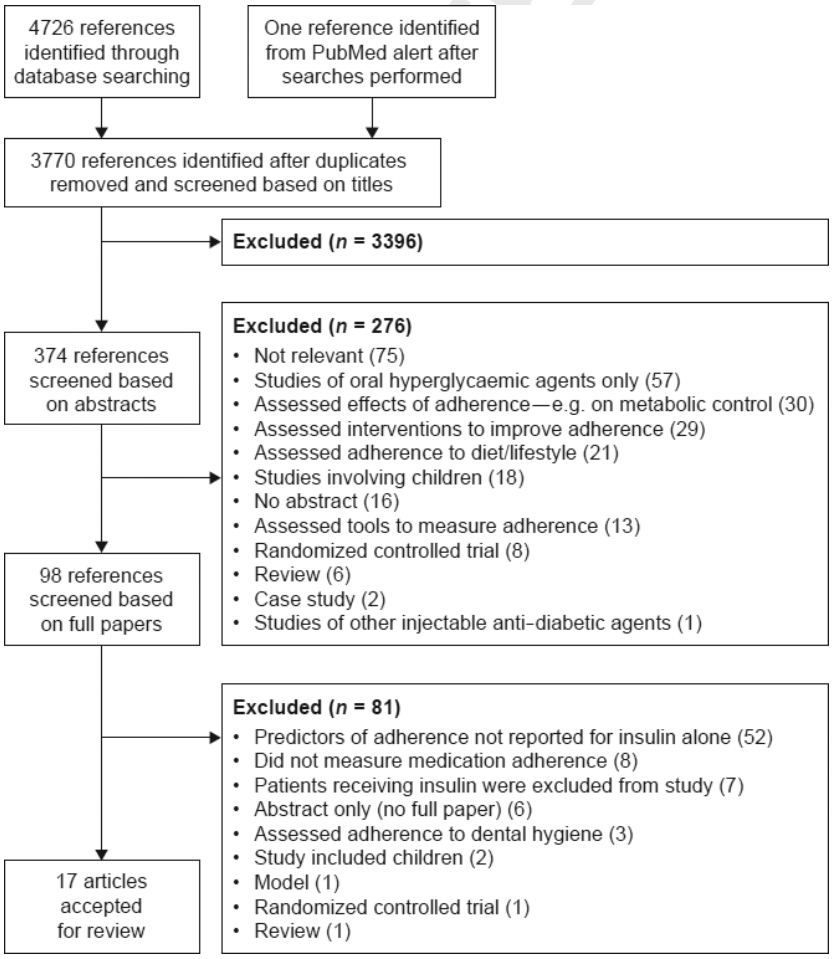

FIGURE 1 Flow diagram of the screening process.

was published after the searches were conducted; it was identified by a PubMed alert, met the inclusion criteria and was therefore included, bringing the total of accepted studies to 17.

Table 1 summarizes the characteristics and key data from the 17 relevant studies. Most studies (13/17) were conducted exclusively in the USA; 10 of them only included patients with Type 2 diabetes, one studied only patients with Type 1 diabetes, five involved patients with Type 1 or Type 2 diabetes and one study did not specify the diabetes type. Six studies used self-reported measures of adherence and 11 used calculated measures of adherence, compliance or persistence. Studies fell into four categories, assessing predictive factors for adherence to insulin therapy (five studies) [21–25], patient-perceived barriers to adherence (four studies) [26–29], adherence following a change in type of insulin or method of delivery (six studies) [30–35] and adherence after a change in insurance scheme (two studies) [36,37]. These categories were chosen based on the findings of the research (i.e. they were not predefined) and are deemed appropriate descriptions of the factors identified in the study. Other than insurance type and delivery device, factors affecting adherence fell into two categories. Factors that predicted adherence (positively or negatively) and that were independent of patients' perceptions of therapy were termed 'factors predictive of adherence to insulin therapy'. Factors related to patients' perceptions of insulin therapy were termed 'patient-perceived barriers to adherence', as all factors identified were negative for adherence. The term also fits with other literature discussing barriers to insulin therapy [15,38].

Predictive factors for adherence to insulin therapy

Five studies investigated predictive factors for adherence to insulin therapy (Table 2) [21–25]. One was a large, retrospective database analysis involving nearly 700 000 patients receiving either oral hypoglycaemic agents or insulin [21]. Results for the total study population (patients receiving insulin or oral hypoglycaemic agents) showed that adherence was lower in individuals who were single, older, female and had lower HbA_{1c} levels (Table 2). The authors stated that results for the insulin-only group were similar to those for the total study population, although statistical analysis was not performed on this patient subgroup.

The other four studies used questionnaires and interviews to assess factors predictive of non-adherence to insulin therapy. In a study of 29 patients with Type 2 diabetes who had recently switched from an oral hypoglycaemic agent to insulin in Mexico, Lerman *et al.* showed that support from a diabetic nurse specialist was a positive predictor for adherence and that most non-adherent patients were women who had previously been non-adherent to oral hypoglycaemic agent therapy [22]. Peyrot *et al.* conducted an internet survey of 502 patients with Type 1 or Type 2 diabetes in the USA and reported that younger patients, students, patients with the highest level of education, those with Type 2 diabetes, patients with the lowest household incomes and individuals with a higher injection frequency were all more likely to skip injections than other people with diabetes [23]. Other factors associated with intentional skipping of injections were: planning days around injections, injections interfering with daily activities, dissatisfaction with injection pain and embarrassment about injections. A third study investigated factors affecting adherence in black patients with diabetes in Washington DC in 1989 [25]. Perceived self-efficacy (how confident patients were about their ability to take medication) and age were strong positive predictors of adherence. Further analysis revealed women were more likely to be adherent if they perceived few barriers to taking their insulin while the presence of barriers to taking insulin did not affect adherence in men. The last study investigated the effect of hypoglycaemia awareness on adherence in patients with Type 1 diabetes. The authors reported that patients with hypoglycaemia awareness were more likely to be adherent to changes in regimens recommended by physicians than individuals without awareness [24]. This study also found adherence to be higher in patients with previous experience of liaison psychiatry and cognitive behavioural therapy than in those without this.

In summary, two studies identified female gender as a predictor of non-adherence [21 22]. Age was identified as a predictor in three studies, although two studies showed that older patients were more adherent to insulin [23,25] and one study showed that younger patients were more adherent [21]. These were the only predictive factors for adherence identified by more than one study.

Patient-perceived barriers to adherence

Four studies assessed patient-perceived barriers to adherence (Table 2) [26–29]. Two involved patients with Type 2 diabetes and two investigated individuals with Type 1 or Type 2 diabetes. Three were small studies, involving fewer than 100 participants taking (or recently discontinuing) insulin therapy [26–28], whereas the fourth enrolled 150−350 insulin-treated patients from eight different countries (1530 patients in total) [29].

Oliveria *et al.* reported that the most common reason for patients discontinuing insulin therapy was a physician advising against such therapy (Table 2) [28]. Other reasons given were that patients used other methods to control diabetes, believed that their diabetes was under control without insulin therapy or did not like injections. Ary *et al.* found that the most common reasons for non-adherence to insulin therapy in patients with Type 2 diabetes were challenging social conditions, such as a spouse not understanding the importance of diabetic control or that individuals were in transit (e.g. in a car, plane or train) [26]. Other reasons for non-adherence included being away from home,

Table 1 Studies of factors affecting adherence to insulin therapy

Reference and country	Type of diabetes	*n*	Age (years)	Study design
Predictive factors for adherence to insulin				
Egede *et al.*, 2011 [21] USA	Type 2	690 968	65.8 ± 11.3	• Large retrospective database study of veterans with Type 2 diabetes followed between 2002 and 2006 • Adherence calculated as medication possession ratio
Lerman *et al.*, 2009 [22] Mexico	Type 2	29	59 ± 8	• Self-reported prospective study of low-income patients with Type 2 diabetes. All patients had recently switched from an oral hypoglycaemic agent to insulin
Peyrot *et al.*, 2010 [23] USA	Types 1 and 2	502	54.9 ± 13.9	• Self-reported cross-sectional internet survey of patients with Type 1 and Type 2 diabetes receiving insulin
Uzoma and Feldman, 1989 [25] USA	Not reported	100	55	• Prospective study of black adults with diabetes attending an inner-city teaching hospital outpatient clinic in Washington DC • Self-reported adherence to insulin therapy. No details of assessment or definition provided
Smith *et al.*, 2009 [24] UK	Type 1	50	Not reported	• Retrospective study of patients with Type 1 diabetes; 31 hypoglycaemic aware, 19 hypoglycaemic unaware • Adherence calculated as proportion of changes to regimen adhered to and percentage of advice from physicians followed
Patient-perceived barriers to insulin adherence				
Oliveria *et al.*, 2007 [28] USA	Type 2	3220 91 discontinuing insulin therapy	82% aged 40–80 years	• Cross-sectional telephone survey of patients with Type 2 diabetes who had discontinued insulin therapy • Persistence calculated from refill records
Ary *et al.*, 1986 [26] USA	Type 2	184 (59 receiving insulin)	Not reported	• Self-reported cross-sectional study in patients with Type 2 diabetes
Broadbent *et al.*, 2011 [27] New Zealand	Types 1 and 2	157 (78 prescribed insulin)	Type 1 diabetes: 43.2 ± 20.6 Type 2 diabetes: 58.0 ± 11.3	• Self-reported cross-sectional study of patients with Type 1 or Type 2 diabetes
Peyrot *et al.*, 2012 [29] China, France, Japan, Germany, Spain, Turkey, UK and USA	Types 1 and 2	1530	60.1 ± 13.7	• Telephone survey of patients with Type 1 or Type 2 diabetes receiving insulin • Self-reported adherence (patients were asked whether they ever missed an insulin dose)
Effects of changing insulin therapy				
Buysman *et al.*, 2011 [31] USA	Type 2	1876	NPH vial: 53.1 ± 15.1 FlexPen®: 54.1 ± 10.1	• Retrospective database analysis of patients with Type 2 diabetes initiating therapy with NPH insulin administered using a vial/syringe or insulin detemir administered using a pen device • Adherence calculated as medication possession ratio • Persistence calculated using refill gaps

Table 1 (*Continued*)

Reference and country	Type of diabetes	*n*	Age (years)	Study design
Lee *et al.*, 2011 [32] USA	Type 2	4088	KwikPen®: 58 Vial: 62	• Retrospective database analysis of patients with Type 2 diabetes assessed before and after initiating therapy with a rapid-acting insulin analogue using either a pen device or vial/syringe • Adherence based on proportion of days covered
Pawaskar *et al.*, 2007 [34] USA	Type 2	Initiating therapy *n* = 1330 Switching device *n* = 1120	Comparison 1: 40.8 ± 16.2 Comparison 2: 52.5 ± 16.9	• Retrospective database study of patients with Type 2 diabetes. Included two comparisons: • patients initiating insulin therapy with either a vial/syringe or pen device (presumably after failing oral hypoglycaemic agent treatment); • patients taking insulin who converted from a vial/syringe to a pen device vs. those who continued to use a vial/syringe • Adherence calculated as medication possession ratio
Baser *et al.*, 2010 [30] USA	Types 1 and 2	1064	Vial: 47.6 ± 15.3 FlexPen®: 47.2 ± 14.9	• Retrospective analysis of patients receiving modern insulin who switched from a vial/syringe to a pen device or continued to use a vial/syringe • Adherence calculated as medication possession ratio
Lee *et al.*, 2006 [33] USA	Type 2	1156	45.4 ± 13.7	• Retrospective study in patients with Type 2 diabetes who had converted from receiving human insulin or insulin analogue administered with a vial/syringe to an insulin analogue given using a pen device • Adherence calculated as medication possession ratio
Xie *et al.*, 2011 [35] USA	Type 2	1280	Insulin glargine: 55.0 ± 10.1 Insulin detemir: 54.8 ± 10.2	• Retrospective database analysis of patients with Type 2 diabetes treated with insulin glargine or insulin detemir administered using a pen device • Adherence calculated as medication possession ratio • Persistence calculated using refill gaps
Effects of changing type of insurance plan Chang *et al.*, 2010 [36] USA	Type 2	211 062	Not reported	• Large retrospective database study of patients with Type 2 diabetes, including 20 173 who switched from a traditional formulary to a value-based insurance design • Adherence calculated as medication possession ratio
Nair *et al.*, 2009 [37] USA	Types 1 and 2	225	49	• Retrospective study of patients with Type 1 and Type 2 diabetes who switched from a traditional formulary to a value-based insurance design at baseline (53 patients were receiving insulin) • Adherence based on proportion of days covered; adherence defined as proportion of days covered > 80%

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Table 2 Predictive factors for non-adherence and patient-perceived barriers to adherence to insulin therapy

Reference	Adherence (*n*)	Factors affecting adherence/non-adherence
Predictive factors for adherence to insulin therapy		
Egede *et al.*, 2011 [21] USA, Type 2 diabetes	Medication possession ratio, 64.6–74.5% (690 968 patients)	• Single status, female gender, older age and lower HbA_{1c} levels were associated with non-adherence • Ethnicity, geographical location and various co-morbidities (including cancer, depression and hypertension) were associated with adherence
Lerman *et al.*, 2009 [22] Mexico	59% (self-reported) (29 patients)	• Having support from a diabetic nurse specialist was a positive predictor of adherence (odds ratio 6.6; 95% CI 1.0–55.7; $P = 0.02$) • Most non-adherent patients were women previously non-adherent to oral hypoglycaemic agent therapy ($P = 0.09$) • Depression was more common in non-adherent women ($P = 0.05$)
Peyrot *et al.*, 2010 [23] Type 2 diabetes	43% (self-reported) (502 patients)	• Patients significantly less likely to skip injections were: older respondents, those who were disabled, those with a higher household income and those who followed a healthy diet ($P \leq 0.02$) • Patients significantly more likely to skip injections were: students, patients with Type 2 diabetes, individuals with the highest level of education and those who needed more injections ($P \leq 0.03$)
Uzoma and Feldman 1989 [25] USA, Type of diabetes not reported	Not reported (100 patients)	• Adherence was significantly related to perceived self-efficacy (patients' confidence in their ability to take medication) and increasing age ($r = 0.42$ and $r = 0.34$, respectively; both $P < 0.001$) in the total study population • For women, adherence was significantly associated with self-efficacy ($P < 0.01$), perceived barriers to treatment, increasing age and satisfaction with social support (all $P < 0.05$) • In men, adherence was significantly associated with self-efficacy, increasing age (both $P < 0.001$) and the number of people providing social support ($P < 0.05$)
Smith *et al.*, 2009 [24] UK, Type 1 diabetes	Not reported (50 patients)	• Patients with hypoglycaemia awareness were more adherent to changes in regimens recommended by physicians vs. patients without hypoglycaemia awareness (87 vs. 54%; $P = 0.046$) • Adherence was significantly higher in patients with previous experience of liaison psychiatry ($P = 0.022$) and cognitive behavioural therapy ($P = 0.042$) than those without this experience
Patient-perceived barriers to adherence to insulin therapy		
Oliveria *et al.*, 2007 [28] USA, Type 2 diabetes	Not reported (34 patients)	• Reasons given for discontinuing insulin therapy: physician advised against insulin therapy (47.1%), use of other methods to control diabetes (17.7%), belief that diabetes was under control (11.8%) and dislike of injections (11.8%)
Ary *et al.*, 1986 [26] USA, Type 2 diabetes	Not reported (59 patients)	• Reasons for non-adherence to insulin therapy: too busy (12%), forgetfulness (12%), negative physical reasons (12%), challenging conditions and lack of support from others (37.5%), in transit (23%), away from home (13%), eating out (10%), on a trip (10%)
Broadbent *et al.*, 2011 [27] New Zealand, Type 1 and Type 2 diabetes	86% of patients claimed they were adherent 'all of the time' (78 patients)	• Adherent patients had lower perceived consequences of diabetes and a higher perception of personal control compared with less adherent patients ($P < 0.05$)
Peyrot *et al.*, 2012 [29] Eight countries, Type 1 and Type 2 diabetes	77% (self-reported) (1530 patients)	• The five most common reasons for non-adherence: too busy (19%), travelling (16%), skipped a meal (15%), stress or emotional problems (12%), embarrassing to inject in public (10%)

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being too busy, forgetting, and eating out or being on a trip. In a study of patients with Type 1 or Type 2 diabetes, Broadbent *et al*. reported that adherent patients had significantly lower perceptions of the consequences of diabetes and higher perceptions of personal control than non-adherent patients [27]. The fourth study involved 1530 patients from China, France, Germany, Japan, Spain, Turkey, the UK and the USA, most of whom (88%) had Type 2 diabetes [29]. The five most common reasons given for non-adherence were: too busy, travelling, skipped a meal, stress or emotional problems and embarrassment about injecting in public. Physicians reported the same factors as the five most frequent reasons given by patients (although rankings of these factors differed for patients and physicians).

There was little consistency in the factors identified in the different studies as being patient-perceived barriers to adherence. The only factor that was identified as a predictor of non-adherence in more than one study was travelling [26,29]. Some similar factors were identified between studies, such as dislike of injections [28], embarrassment of injections [29], challenging social conditions [26] and stress or emotional problems [29]. There were no other similarities between studies in the factors identified as being perceived barriers to adherence.

Type of delivery device and type of insulin

Three studies compared adherence in patients initiating insulin therapy with either a pen device or a vial/syringe (Table 3) [31,32,34]. Two of these showed that adherence (measured as either medication possession ratio or proportion of days covered) was significantly higher in patients beginning insulin therapy with a pen than with a vial/syringe [31,32] and one showed no difference between groups [34]. Buysman *et al*. also showed that the discontinuation rate was significantly lower among patients who had initiated therapy with a pen instead of a vial/syringe [31].

Three studies investigated the effect on adherence to insulin therapy of switching from using a vial/syringe to using a pen device (Table 3). Two studies showed significant improvements in medication possession ratio following switching to a pen [30,33].The third study reported a significant decrease in adherence following switching to a pen compared with continuing to use a vial/syringe, but there was a significant improvement in adherence to all medications following switching [34]. A further study reported that adherence and persistence were both higher in patients initiating therapy with insulin glargine compared with insulin detemir (two different long-acting basal insulin analogues) when both were administered using a pen device [35].

Results from this category of studies were largely consistent, and showed that patients were more likely to initiate, and remain adherent to, insulin therapy if they were treated with a pen device rather than a vial/syringe.

Type of insurance plan

Two studies, both conducted in the USA, assessed the effects of changing the type of insurance plan on adherence. Both studies showed improved adherence to insulin therapy after changing from a traditional three-tier formulary to a value-based insurance design (VBID), an insurance scheme in which co-payments are reduced or even eliminated for highly effective preventive medications [36,37]

The first showed that adherence to insulin therapy improved over the first year in patients joining a value-based insurance design and declined over the same period in those who remained on the traditional formulary [36]. The

Table 3 Adherence in patients initiating therapy with a vial/syringe or a pen device or switching from a vial/syringe to a pen device

Reference and country	Adherence measure (*n*)	Adherence with vial/syringe	Adherence with pen device	*P*-value
Initiating insulin therapy				
Buysman *et al*., 2011 [31] USA	Medication possession ratio (1876)	38%	53%	< 0.001
Lee *et al*., 2011 [32] USA	Proportion of days covered (4088)	45.2%	54.6%	< 0.001
Pawaskar *et al*., 2007 [34] USA	Medication possession ratio (1330)	50%	53%	
Switching from a vial/syringe to a pen device				
Baser *et al*., 2010 [30] USA	Medication possession ratio (1064)	13%[a]	22%	< 0.001
Lee *et al*., 2006 [33] USA	Medication possession ratio (1156)	62%[b]	69%	< 0.01
Pawaskar *et al*., 2007 [34] USA	Medication possession ratio (1120) Insulin therapy All medication†	56%* 90%*	45% 92%	< 0.05 < 0.05

*Patients remaining using vial/syringe.
†Adherence before switching to a pen device.

initiation rate for insulin therapy was also significantly higher at 1 year in the value-based insurance design group than in the control group. In the second study, the entire study population changed to a value-based insurance design from a traditional formulary at baseline. Adherence to insulin therapy was significantly higher at 1 and 2 years compared with baseline [37]. However, the proportion of patients classified as adherent (i.e. proportion of days covered > 80%) remained at approximately 20% after switching insurance plan. The results of both studies suggest that adherence is improved when the financial burden to the patient is reduced.

Study quality

Overall, the studies were judged as being of poor quality, with 9/17 (53%) of the studies being rated as poor for at least one category as measured using the Effective Public Health Practice Project tool (see also Supporting Information, Table S3). The most common reasons for being of poor quality were that non-validated tools were used to assess adherence and that the study used a volunteer population (rated as weak for the selection bias section). Assessment of withdrawals and dropouts was not appropriate for the majority of studies as they were retrospective studies where inclusion criteria stated that patients needed data available for the duration of the study, or because they were surveys were performed at a single time point.

Conclusions

This systematic review identified 17 studies that reported on factors affecting adherence to insulin therapy. Self-reported rates of adherence ranged from 43 to 86%, and mean medication possession ratio was less than 80% in all studies examining this measure, confirming that adherence to insulin therapy is generally poor. Identified factors associated with non-adherence fell into four categories: predictive factors for non-adherence, patient-perceived barriers to adherence, type of delivery device and financial burden to the patient.

Four studies investigated patient-perceived barriers to adherence to insulin therapy [26–29], although there was little consistency in results; the only factor identified by more than one study was travelling [26,29]. All studies used self-reported questionnaires, so results may reflect different methodology rather than differences between patient populations. Notably, fear of weight gain and hypoglycaemia, which are frequently cited as reasons against initiating insulin therapy [15,38], were not mentioned as barriers to adherence, suggesting that these factors may be less important once treatment has started. Dislike of injections and feeling embarrassed about injecting in public were given as reasons for non-adherence, and may correspond to the stigma of injections, which has been cited as a barrier to beginning insulin treatment [14,15]. Other perceived barriers included practical difficulties of fitting injections into patients' busy routines and the perception that insulin therapy may not be necessary. Predictive factors for non-adherence included female sex (two studies) [21 22] and age (three studies), although younger patients were more adherent in one study [21] and less adherent in the other two studies [23,25]. Although several other factors were identified as predictive of non-adherence, none was identified in more than one study.

Switching to, or initiating therapy with, insulin administered by a pen device (instead of a vial/syringe) improved adherence in four of the five studies investigating this factor [30–33]. Pens have been shown to reduce injection pain, help overcome stigma and fear of injections, and are associated with greater treatment satisfaction and quality of life than other devices [39,40]. One third of patients in Europe and 85% of patients in the USA do not use pens [41], suggesting that increased use of pen devices might improve adherence.

Changing to an insurance scheme in which co-payments are reduced increased adherence in two studies conducted in the USA [36,37], suggesting that affordability of medication may have a significant impact on adherence. This is in agreement with a recent literature review of 66 studies from the USA or Canada evaluating the relationship between changes in cost sharing and adherence to interventions for various disorders, including cardiovascular disease, diabetes and mental health problems [42]. Most studies (85%) showed that increasing the patient share of medication costs was significantly associated with decreased adherence. Similarly, a recent Canadian survey found that 9.6% of respondents who had received a prescription in the previous year reported that out-of-pocket expenses had led to non-adherence [43]. The patient share of the cost of insulin therapy is therefore likely to be an important factor leading to non-adherence when patients have to pay a large proportion of treatment costs and may deny access to therapy for some patients. Indeed, the cost of managing insulin therapy (including the cost of syringes and monitoring tests), together with issues affecting the availability of insulin, are recognized to be major factors influencing insulin use in sub-Saharan African countries; in 2003, the International Diabetes Federation estimated that 80% of people with diabetes in these countries were unable to afford insulin and syringes [44]. Lack of accessibility to health services and inadequate follow-up are additional factors affecting the use of insulin in developing countries such as India [45]. Pricing issues and inadequate reimbursement across developing countries may add further barriers to access to insulin. However, it could also be argued that, if patients have to pay for their medication, they will be more likely to be adherent in order to gain the most benefit from their medication, although this is not borne out in the results reported here.

Key predictors of adherence/non-adherence are summarized in Table 4, along with potential strategies to improve

Table 4 Summary of predictive factors for adherence to insulin and strategies for improving adherence to insulin

Positive predictors of adherence to insulin	Negative predictors of adherence to insulin	Strategies for improving adherence
Changing insulin therapy • Switching from a vial/syringe to a pen device [30,33] • Initiating insulin therapy with a pen device instead of a vial/syringe [31,32,34]	• Switching from a vial/syringe to a pen device [34]	• Increased use/availability of pen devices
Changing type of insurance plan • Switching from a traditional formulary scheme to a value-based insurance design [36,37]		• Reduce the financial burden of insulin therapy to the patient
Predictive factors for adherence to insulin • Older age [23,25] • Support from a diabetic nurse specialist [22] • Physical disability [23] • Higher household income [23] • Following a healthy diet [23] • Perceived self-efficacy [25] • Hypoglycaemia awareness [24] • Previous experience of liaison psychiatry [24] • Previous experience of cognitive behavioural therapy [24]	• Older age [21] • Female gender [21,22] • Single status [21] • Lower HbA_{1c} levels [21] • Being a student [23] • Having the highest level of education [23] • Needing a large number of injections [23] • Type 2 diabetes (vs. patients with Type 1 diabetes) [23]	• Provide additional medical support to patients (e.g. nurses, psychiatrists) • Educational programmes to increase awareness of diabetes • Develop therapies that allow for fewer injections and increased flexibility in treatment regimen
Patient-perceived barriers to insulin adherence • Lower perceived consequences of diabetes [27] • Higher perception of personal control [27]		• Provide additional medical support to patients (e.g. nurses, psychiatrists)

the initiation of, and adherence to, insulin therapy. The patient-perceived barriers identified indicate that many patients have concerns regarding injections and the need to fit them into their daily life, suggesting that adherence may be improved by therapy allowing for greater flexibility in dosing regimen. Studies suggest that pen devices may alleviate issues associated with injections, while insulin analogues and newer anti-hyperglycaemic agents, such as the incretin mimetics, may help to reduce concerns of hypoglycaemia and weight gain, which are frequently perceived as barriers to initiating therapy. The identified predictors of non-adherence indicate that different approaches may be required for particular patient subgroups, such as women and older patients, and that social and medical support may be important for improving adherence. Better education about diabetes at all levels (including healthcare providers, patients and their families) is clearly necessary to ensure that patients understand the importance of achieving good metabolic control. Two recent meta-analyses assessing a total of 51 randomized controlled trials have shown that diabetes self-management education (DSME) programmes encouraging close interaction between patients and healthcare providers improve glycaemic control, disease understanding and diabetes self-management [46,47]. The American Association of Diabetes Educators and the American Diabetes Association have been producing guidance on diabetes self-management education programmes for several years, the most recent of which was recently published [48,49]. Despite these efforts, rates of adherence to insulin in the USA reported in this review were poor, suggesting that considerable work is still required to achieve good self-management practices. Cost to the patient is evidently a major concern in countries where individuals have to pay a significant proportion of medical costs, and access to healthcare is a further factor, especially in developing countries. Improved access to healthcare (through reimbursement schemes and the work of public health authorities) is required to enable all patients to receive appropriate insulin therapy.

To our knowledge, this is the first comprehensive systematic review to focus solely on factors affecting adherence to insulin therapy; it has been conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Despite the rigorous methodology used, the study has several limitations owing to the small number and poor quality of relevant studies identified. Only eight studies involved more than 1000 insulin-treated patients, five included data for fewer than 100 individuals receiving insulin and nine out of 17 were rated poor for at least one category as measured using the Effective Public Health Practice Project tool. The only consistency in study designs

and results were for studies investigating the impact of delivery devices on adherence, for which we considered that it might be feasible to perform a meta-analysis, although, as stated, it was not our intention to perform a meta-analysis. There was very little consistency in methodologies or results among studies assessing patient-perceived barriers to, or predictive factors for, non-adherence. The description and rigor of self-reported measures of adherence were generally poor and no statistical analyses were performed in two of the studies. All but four studies were conducted solely in the USA, precluding evaluation of differences between countries and cultures. We had also hoped to assess adherence across time to evaluate the impact of technologies/treatments that had been developed specifically to improve adherence. Unfortunately, our searches identified only two studies from the 1980s [25,26] and all other studies were published from 2006 onwards preventing this analysis. Another possible limitation of the study is the potential bias introduced by excluding non-English studies. This has been examined previously in a study comparing the treatment effect estimates from 50 meta-analyses across several therapy areas comprised of both English and non-English studies [50]. Results for the full analyses were found to be similar to those obtained by excluding non-English studies, although the precision of the estimates was sometimes reduced. This suggests that the bias introduced by excluding non-English studies in the present review is unlikely to affect the findings of the study.

The results of this review suggest that factors affecting adherence to insulin therapy may differ from those influencing initiation of therapy and need to be given serious consideration in order to improve long-term outcomes for patients with diabetes. Additional real-world studies are required to investigate such factors further, particularly in countries other than the USA. Use of a consistent study design would allow meta-analyses to be conducted, which could provide further information regarding factors that influence adherence. The results from such studies should help healthcare professionals to develop strategies for improving adherence to insulin therapy worldwide, and hence avert the epidemic of chronic diabetes complications and the subsequent socio-economic burden that is anticipated as a result of the increased global prevalence of diabetes.

5 Funding sources

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Competing interests

JJG has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme and Bristol-Myers Squibb, and as a speaker for Servier. He has also received unrestricted grants to support research studies from Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme and Bristol-Myers Squibb. KK sits on the advisory boards of Novo Nordisk, Eli Lilly MSD, Bristol-Myers Squibb and Roche. He has received funding for research from The Diabetes Research Network and The University of Leicester, and has been a speaker for Novo Nordisk, Eli Lilly, Sanofi-Aventis, Novartis and Boehringer Ingelheim Lilly. MJD has acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme and Roche, and as a speaker for Servier. She has received grants in support of investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Pfizer, Merck Sharp & Dohme, GlaxoSmithKline and Servier. RH is an employee of Oxford PharmaGenesis™ Ltd, which has received project funding from Novo Nordisk Region International Operations. VM has acted as a consultant and speaker, and has received grants, in support of investigator-initiated trials, from Novo Nordisk, Lifescan, Johnson & Johnson, Merck Sharp & Dohme, Sanofi-Aventis, Roche Diagnostics and Abbott Nutrition International. LG has nothing to declare.

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Table S2. Search terms and results in EMBASE.
Table S3. Assessment of study quality.

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Query reference	Query	Remarks
1	AUTHOR: this has been suggested as a short title. Please amend if desired (note that a short title should not exceed 75 characters including spaces)	
2	AUTHOR: journal style is to have a minimum of abbreviations, therefore the abbreviations used in this article have been written in full throughout. Please check that this has been done correctly and appropriately	
3	AUTHOR: please check this section of text for sense. Does this mean that early and appropriate initiation of insulin therapy combined with high levels of adherence to treatment appears to be an effective tool? Rather than the two aspects being separate tools?	
4	AUTHOR: the second footnote symbol has not been found in the table (originally a superscript 'b'). Please indicate where the corresponding symbol should be placed	
5	AUTHOR: please note that the sections of Author contributions, Acknowledgements and Competing interests have been changed to Funding sources, Competing interests and Acknowledgements in accordance with journal style. Please check that this has been done appropriately	
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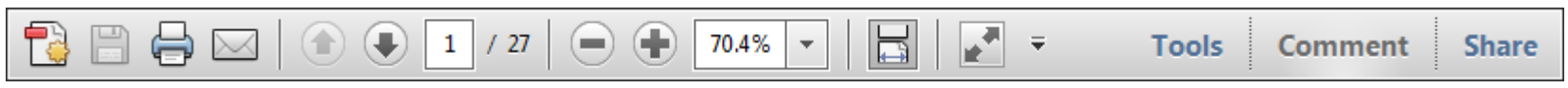

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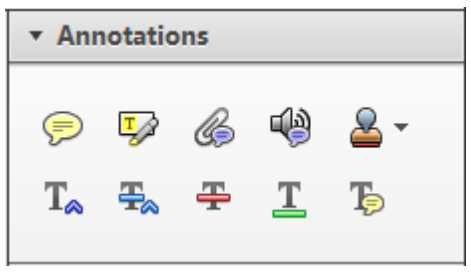

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- Click on the Replace (Ins) icon in the Annotations section.
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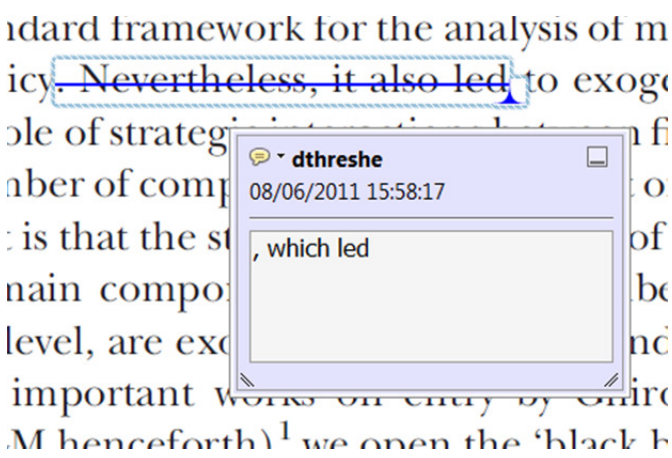

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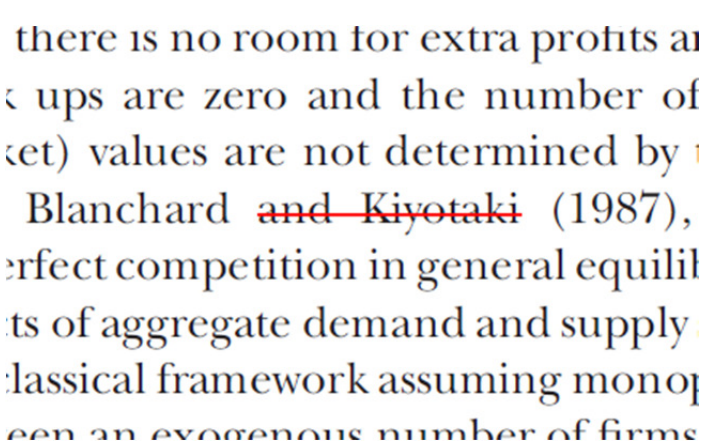

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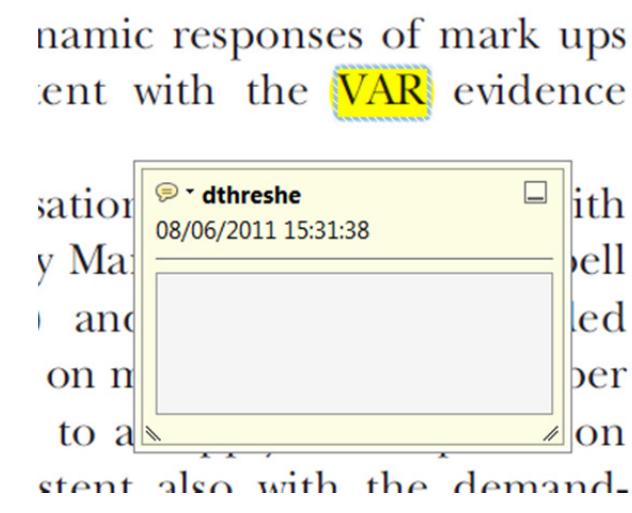

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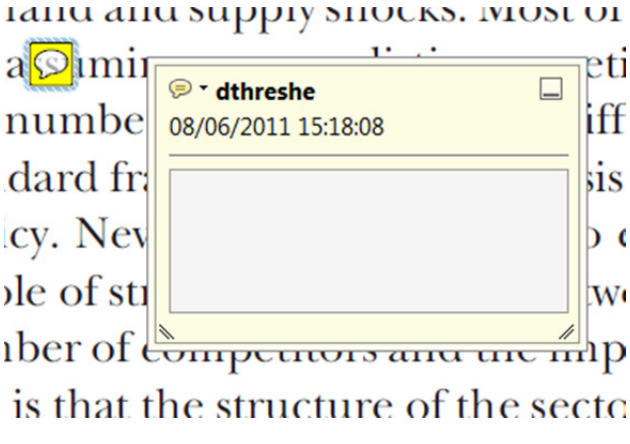

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5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

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- Click on the Attach File icon in the Annotations section.
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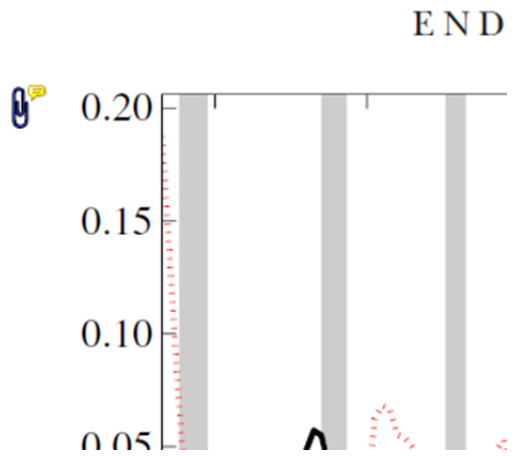

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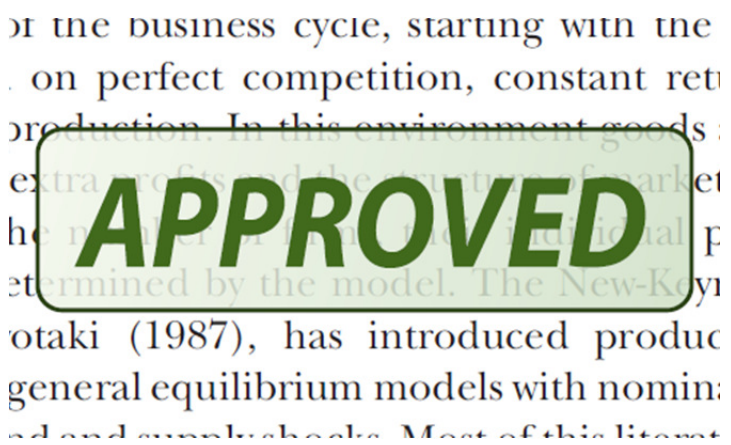

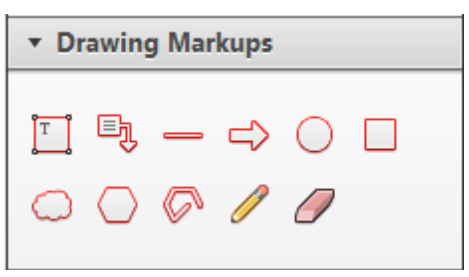

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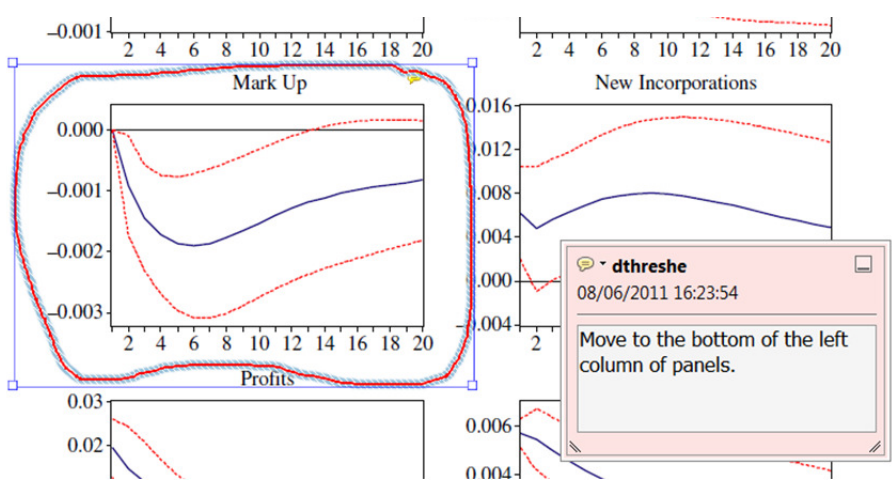

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