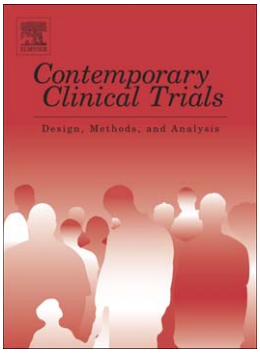

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Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: A review of current practice

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Abstract

Background: Data suggest that certain psychological interventions can induce harm in a significant number of patients. While the need for adequate reporting of harms in clinical trials has repeatedly been emphasized, it is uncertain whether such information routinely is collected and reported in trials within this research field.

Method: We used the two major databases in clinical psychology and medicine (PsycINFO and PubMed) to identify original publications from 2010 reporting randomized controlled trials of psychological interventions for patients with mental and behavioral disorders. Two reviewers searched the full-text reports for information about monitoring of adverse events, side effects, and deterioration.

Results: Totally 132 eligible trials were identified. Only 28 trials (21%) included information that indicated any monitoring of harms on patient level. Four (3%) of these trials provided a description of adverse events as well as the methods used for collecting these data. Five of the trials (4%) reported adverse events but gave incomplete information about the method. An additional four reports (3%) briefly stated that no adverse events occurred, whereas 15 trials (11%) only provided information on deterioration or indicated monitoring of deterioration. The probability of including harm-related information was related to the journal impact factor.

Conclusion: Important information about harms is not reported systematically within this research field, suggesting that the risk of reporting bias is nontrivial in conclusions about the risk-benefit ratio of psychological treatments.

Guidelines on how to define, detect, and report harms related to psychological interventions could facilitate better reporting.

Key words: Adverse Effects; Behavioral Disciplines and Activities; Psychotherapy; Systematic Review; Randomized Controlled Trials

Introduction

An impressive number of randomized controlled trials (RCTs) of psychological interventions are published each year: In a review of the quantity, scope and characteristics of recent RCTs of psychological interventions for patients with various medical conditions, we found no less than 295 primary reports published during the single year of 2010 [1]. The reports spanned a wide range of interventions, outcomes and conditions. Unfortunately, the usefulness of many trials within this research field is limited by an unsatisfactory quality of reporting [1, 2].

Adequate reporting of both benefits and risks is of particular interest to patients, clinicians, policymakers, and other stakeholders. This information is required in order to enable the individual patient to make an informed choice and facilitate well-founded clinical decisions. Although an increasing number of RCTs show that psychological interventions can be successfully applied to a wide range of mental disorders [3, 4], less is known about potential harms (i.e., adverse events, side effects, and symptom deterioration). However, some psychological treatments might induce harm in a significant number of patients [5-8]. A review from 2007 lists some bona fide therapies that are potentially harmful, such as critical incident stress debriefing, grief counseling for normal bereavement, and boot camp interventions for conduct disorder [5]. The author stresses that the potential harms are likely to be multidimensional, and not merely restricted to deterioration of target symptoms. Furthermore, treatments that are beneficial for most patients might produce unexpected adverse effects in a small number of

individual under specific circumstances. Equally important, the safety profile might be an advantage of psychological treatments compared to some pharmacological alternatives.

The need for better reporting of harms in clinical trials has repeatedly been emphasized [9-11]. The extended Consolidated Standards of Reporting Trials Statement (CONSORT) [10] recommends that the method section should list the addressed adverse events with definitions and clarify how harms-related information was collected. CONSORT also suggests that the results section should provide information about the absolute risk of adverse events. Also, the American Psychological Association's Working Group on Journal Article Reporting Standards recommends that all important adverse events or side effects should be reported [12]. However, there are indications that such information is sparse in trials of psychological interventions [13, 14]. One reason for this could be that psychological interventions often are considered to be safe, and consequently researchers might not prioritize monitoring of harms. In addition, there is a lack of clear guidelines on how to define, categorize, identify and report harms within this research field [15, 16].

Currently, the development of new standards for reporting trials of social and psychological interventions, the Consolidated Standards of Reporting Trials Statement for Social and Psychological Interventions (CONSORT-SPI), are underway [17]. We intended to contribute to the ongoing work by reviewing the monitoring and reporting of harms in recent trials, across the full range of psychological interventions for mental and behavioral disorders. The aim was to provide a snapshot of current practice in order to detect areas in need of improvement and identify good examples.

Method

Protocol and registration

The present review is part of a project aiming to investigate the quantity, scope and characteristics of recent RCTs of psychological interventions for patients with various medical conditions [1]. The project was initiated by the Swedish Council on Health Technology Assessment, which is a public authority that has the mandate of the Swedish Government to comprehensively assess healthcare technology from medical, economic, ethical, and social standpoints (www.sbu.se/en). No international database of prospectively registered protocols for this specific type of systematic reviews was found at the time when this review was planned.

Eligibility criteria

Type of reports and study design

We considered primary reports in English of RCTs published in print or online in peer-reviewed journals during the calendar year of 2010. We decided to limit our search to publications no earlier than 2010 in order to collect data in line with current practice, and 2010 was the most recent year for which the database indexing was complete at the time of the search. We excluded secondary publications, follow-ups of previously published trials and RCTs identified as a pilot or exploratory study by the authors, thus limiting the review to primary reports of full-scale trials.

Participants: Participants of any age that were diagnosed with a mental or behavioral disorder according to the International Classification of Diseases and

Related Health Problems version 10 (ICD-10) [18] or the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised (DSM-IV-TR) [19].

Interventions: Any psychological intervention, defined as a method to improve health by means of strategies that induce changes in a patient's cognitions, emotions, and behaviors according to an explicit psychological theory. If a report did not include any explicit explanation of mechanisms of change, we judged the similarity of the intervention with other established psychological treatments. Further, the effects of a psychological intervention must have been evaluated for the study to be eligible for inclusion. Accordingly, studies were excluded if the intervention included a psychological component only as part of a treatment package (i.e., multimodal treatment) and the effects of the psychological component were not evaluated specifically. Trials in which pharmacological treatment was actively introduced or withdrawn in at least one treatment arm were excluded, due to differences between pharmacological and behavioral interventions in how harms are reported and monitored. Trials including participants with ongoing medication or introducing or withdrawing medication for some of the participants in at least one condition (e.g., treatment as usual or prescription of medication if desired by the participants) were not excluded.

Comparators: Any non-pharmacological comparator.

Outcome measure: Any health-related outcome measure.

Information sources

The electronic databases PubMed (NLM) and PsycINFO (EBSCO) were searched on 15 November 2011. The searches were limited to articles that were indexed

as published in a journal or online ahead of print between 1 January 2010 and 31 December 2010.

Search

The search strategy for PubMed was: psychotherapy [MeSH] OR nursing [MeSH] OR psychology, applied [MeSH] OR rehabilitation [MeSH] OR preventive health services [MeSH] OR behavioral medicine [MeSH] OR psychosomatic medicine [MeSH]. The search was filtered by publication date 2010-01-01 to 2010-12-31 and by publication type (RCT). The search in PsycINFO used the following subject headings (including subheadings): healthcare psychology, behavioral medicine, rehabilitation, psychosomatic health, habilitation, prevention, psychotherapy, health education, clinical psychology, health behavior, lifestyle changes, skills learning and early intervention. The search was limited to reports published between 2010-01-01 and 2010-12-31 and treatment outcome/clinical trials.

Study selection

Two independent reviewers assessed titles and abstracts of all identified reports for eligibility. Disagreements between reviewers were resolved by consensus. The reports obtained in full-text were divided between the four reviewers. One reviewer checked each report in detail for inclusion/exclusion criteria. Suggestions for exclusion at this stage were discussed by all four reviewers and resolved by consensus.

Data extraction

All eligible reports were searched for information about monitoring of harms (adverse events, side effects and deterioration). First, one reviewer (IA or UJ)

searched the PDF-files for the following words with the find command in Adobe® Reader® X: harm, deteriorat (truncated to include deterioration and deteriorate), “side effect”, “side effects”, side-, worse, safe, adverse, and impair. Then the reviewer searched the results section of all reports manually for any information about harms. If a report included information about monitoring of harms, the methods section was searched for information about how these were defined and measured. In order to ensure the integrity of the data, a second reviewer (UJ, IA, FA, or TP) also screened the results section of each included report for relevant information. Four reports could only be obtained as a printed copy, and were read in full by one reviewer.

All information about monitoring of harms was extracted and summarized by one reviewer (UJ) and audited by a second reviewer (FA). In addition, information about diagnosis, treatment, age span, continent where the trial was conducted, and the impact factor for 2010 of the journals in which the reports had been published was extracted and audited.

The primary diagnosis for which the study sample had been selected was categorized according the diagnostic categories of the ICD-10 as follows: *dementias* [F00-F03]; *mental and behavioural disorders due to psychoactive substance use* [F10-F19]; *schizophrenia* [F20]; *mood [affective] disorders* [F30-F39]; *anxiety disorders (including obsessive-compulsive disorder)* [F40-F42]; *reaction to severe stress, and adjustment disorders* [F43]; *eating disorders* [F50]; *specific personality disorders* [F60]; *pervasive developmental disorders* [F84]; *any other mental and behavioural disorder or intentional self-harm* [remaining codes in Chapter V and X60-X84].

The type of psychological interventions was categorized primarily by using the

category reported by the study authors. If no such identifier was found we categorized the intervention according to the authors' description of the intervention or the references used in the description. We categorized interventions according to established treatment paradigms where possible. Interventions that did not match a specific paradigm were categorized according to their main components. Interventions that neither fit an established paradigm nor included such components were categorized according to how the expected change was described to occur by the authors (e.g., by means of change in cognitions, social relations, motivation, or behaviors).

The study participants were categorized as children/adolescents if only ages 0–19 were eligible, elderly if they were over 60 years of age, or else as adults. The continents where the trial was conducted were categorized as Africa, Asia, Europe (including Russia), North America, Oceania, and South/Central America. If the report did not explicitly state where the trial was conducted, we assumed that it was in the country of the Ethical Review Board or the authors' university. The journals' impact factors were retrieved from the 2010 Journal Citation Reports® (Thomson Reuters, 2012).

Data analysis

The median and the interquartile range (IQR) were calculated for ordinal and interval data. For nominal variables the proportions were reported. Frequency distributions were compared by means of the Mann-Whitney *U* test. IBM SPSS Statistics v.20 was used for all analyses.

Results

Study selection

The search provided a total of 3696 citations. Of these, 3482 were discarded after review of the titles and abstracts. The remaining 214 reports were retrieved in full-text. At this stage, another 82 reports were excluded because they did not meet the eligibility criteria (Appendix). A total of 132 reports were included in the synthesis (Figure 1) (Appendix).

Figure 1 about here

Characteristics of the included studies

The included reports spanned a wide range of mental and behavioral disorders, with the most frequent being anxiety disorders (23%), mood disorders (14%), substance use disorders (11%), dementias (8%), and reaction to severe stress and adjustment disorders (8%)(Table 1).

Treatments based on cognitive behavioral therapy were assessed in of 69 (52%) of the trials, while 15 (11%) trials assessed cognitive training programs and 9 (7%) assessed motivational interviewing. A number of other treatments were evaluated in a smaller proportion of the trials, including psychodynamic therapy, mindfulness, family therapy, expressive therapies and social skills training.

The trials were mainly conducted in Europe (41%), North America (41%), or Oceania (9%). Fewer were conducted in Asia (6%) and South/Central America (2%), while only one single trial was conducted in Africa (1%).

In the majority of the trials the participants were adults (73%), while 19% of the trials pertained to children or adolescents and 8% to the elderly. The median number of participants in the treatment condition of the trials was 37, with an interquartile range (IQR) of 23 to 57.

The journals publishing the reports had a median impact factor of 2.96 for the year 2010, with an IQR of 2.12 to 5.20.

Reporting of harms

Only 28 (21%) reports included information that indicated that adverse events, side effects or deterioration were monitored during the trial.

Four reports provided a complete report of occurring adverse events as well as the methods used for collecting these data [20-23]. In a trial of cognitive-behavioral therapy for posttraumatic stress disorder (PTSD) in children [20], an 8-item checklist was designed to measure adverse events. The checklist included items for “suicidality”, “homicidality”, “grave disability”, “hallucinations”, “worsening of any old symptom”, “appearance of any new symptom”, “exposure to new domestic violence”, and “a category for other”. In a trial of behaviour therapy for children with Tourette disorder [21], the therapists asked the participants each session about recent health complaints, behavioral changes, visits for medical/mental health care, need for concomitant medications, change in on-going medications, and hospitalizations, and offered the opportunity for spontaneous report of any other problem. One trial aimed to systematically assess adverse effects in exposure treatment of PTSD related to chronic and early-life trauma [22]. PTSD symptoms during the previous week were assessed at the end of every other session to elicit information about symptoms during

exposure. Clinically meaningful deterioration was defined as a post-treatment score exceeding the baseline score by at least one standard deviation of the difference between two repeated administrations. Finally, in a 2-year trial of a family intervention in severe schizophrenia [23], monthly evaluations were made by a psychiatrist not involved in the treatment in order to determine the possibility of clinical relapse and major incidents.

Five trials provided information about adverse events in the results section but had missing or incomplete information about how the data was collected [24-27], or how the adverse events were defined [28]. Four reports only briefly stated in the results section [29], methods section [30, 31] or the discussion [32] that no adverse events occurred or were observed, without providing information about how these adverse events were defined or monitored.

Fifteen reports did not report adverse events but included information about deterioration, which was defined and measured in various ways. In five trials [33-37], a reliable change index [38] was used to identify whether a proportion of participants had deteriorated. Six trials [39-44] used the clinical global impression of improvement (CGI-I) [45], which is a clinician-administered scale ranging from 1 (very much improved) to 7 (very much worse). However, only three of these reports included information about the proportion of participants that deteriorated [39, 40, 44]. Two trials evaluated an intervention for patients with dementia and their caregivers [46, 47], and assessed change in caregivers on a scale ranging from 1 (got much worse) to 5 (improved a lot). Clinically significant change in the patients was defined as a change of 0.5 standard deviations or more in one of these trials [46]. A trial of imagery rehearsal for posttraumatic nightmares [48] defined deterioration as a change of two or more

for the number of nights with nightmares and for the weekly number of nightmares. Finally, a trial that compared an alternative therapy (meridian-tapping) with progressive muscle relaxation for obsessive-compulsive disorder [49] presented the proportions in each group with 10%, 20%, and 30% worsening in core symptoms.

In total, 104 (79%) reports did not indicate that adverse events, side effects, or deterioration had been monitored. One of these reports [50] stated in the methods section that the treatment was "not deemed harmful". Another report [51] informed that although data on side effects or adverse events data were not formally collected, none of the subjects reported any negative events during the study. A few of the reports provided information about dropout due to deterioration, but did not include information about monitoring of harms in the participants that continued the trial.

The impact factors of the journals in which the reports had been published were higher for the reports with information about monitoring of harms (median = 3.97; IQR = 2.96 to 5.23) than for the reports without such information (median = 2.96; IQR = 2.00 to 5.09), U=1 762, p<0.05.

Table 1 about here

Discussion

The present review of recent trials of psychological interventions for mental and behavioral disorders clearly demonstrates that adequate information about monitoring of harms rarely is provided. With few exceptions, even the trials that included information about adverse events had incomplete descriptions of how these adverse events were defined and monitored. It is possible that adverse events actually were monitored more frequently than what is evident from the reports, but were not reported if no adverse events occurred. However, even if we assume that the researchers would have reported any observed harms, we cannot know how systematically they monitored and recorded this.

Despite the low rate of reporting, a few commendable examples were identified in the present review. A checklist of adverse events was developed for one of the trials [20]. In another trial the therapists asked about adverse events each session [21]. The participants in yet another trial, spanning over two years, were assessed for relapse and major incidents every month [23]. This kind of active and regular monitoring might be crucial, in order to obtain valid information. Indeed, a recent study suggested that therapists have considerable difficulty recognizing client deterioration, challenging the assumption that routine clinical judgment is sufficient [52]. This also suggests that the practice of monitoring deterioration should be routinely adopted in trials of psychological treatment.

There was notable variation across disorders in the proportion of publications that reported on harms. PTSD trials were by far most likely to include harm-related data. There are two plausible reasons for this: First, within the field of trauma several well-known ineffective and potentially harmful treatments have been and still are used [5], which probably have increased the sensitivity for

these issues within this particular field. Second, although exposure-based PTSD treatments use the same methods as other exposure treatments the obviously distressing nature of imaginal exposure (e.g., retelling a rape) has compelled researchers to ensure the safety of the participants [53].

Several authors have recently brought attention to the neglect of potential harms related to psychological interventions [6-8, 14, 54]. There are a variety of possible reasons for this neglect [14]. The methods used in pharmacological trials might not be fully applicable to this field [16], and the lack of clear definitions could be a decisive factor. It is unclear what unwanted effects one may expect, when they are likely to appear, how the patient should be prompted to report such events, and if other individuals besides the patient are at risk of negative consequences. The complexity of the interventions and outcomes of psychological interventions thus call for conceptual definitions of potential harms, in order to facilitate adequate and unambiguous reporting.

Ongoing work offers hope for improvement in this respect. For instance, Linden recently proposed a theoretical framework for side effects of psychotherapy [55]. In his paper, Linden presents definitions of unwanted events, treatment-emergent reaction, adverse treatment reaction, malpractice reaction, treatment non-response, deterioration of illness, therapeutic risk, and contraindications. This terminology could be useful in the process of systematizing observations from RCTs. The distinction between treatment-emergent reactions linked to the treatment and unwanted events unrelated to the treatment is central. A few reports in the present review indicated that such judgments were made, in some cases by an Institutional Review Board [27] or an independent Data Monitoring Committee [25].

Some lessons could also be learned from pharmacological research, although the reporting of safety data has been found unsatisfactory in pharmacological trials as well [11, 13, 56, 57]. Most adverse events are detected and recorded only if they occur early during pharmacological treatment, or if they were anticipated at the phase of trial planning [58]. A recent systematic review of the reporting of adverse effects in RCTs of antidepressants for anxiety and depressive disorders found that structured assessment methods (e.g., checklists or self-rating scales) yielded considerably higher rates of reported symptoms as compared to unstructured assessment methods [57]. However, certain unstructured approaches, such as open-ended questions, can be crucial in evoking patient reports of rare but serious adverse events. Taken together, this underscores the importance of using systematic ascertainment strategies when monitoring harm-related data in clinical trials.

Another approach from pharmacological research that might be adopted is the practice of collecting important patient safety data in post-marketing naturalistic studies. These study designs, in real-world clinics and with larger samples, allow for collecting data on adverse events not found in RCTs such as rare events, long-term effects, events that occur after treatment discontinuation, as well as events incurred by malpractice [59]. In addition, safety monitoring could be prioritized in pilot and case studies of new interventions.

Awaiting consensus on how to monitor and report harmful effects of psychological interventions, more general ethical principles can provide guidance for Ethical Review Boards and researchers. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects [60]. The

declaration postulates that measures to minimize risks must be implemented and that the risks must be continuously monitored, assessed and documented by the researcher. The Declaration of Helsinki also states that all vulnerable groups and individuals should receive specifically considered protection, which further emphasizes the need of safety monitoring in research involving participants with mental and behavioral disorders.

One possible way forward could be that Ethical Review Boards require that investigators provide a detailed plan for how harms will be detected, how often they will be assessed and how they will be reported. We would generally recommend active and regular monitoring. In order to identify deterioration on continuous outcome measures, a reliable change index such as that devised by Jacobson and Truax [38] might be used. For measurement of other adverse effects, available instruments such as the ones recently proposed by Linden [55] and by Parker and colleagues [61] could be applicable. Instruments might also have to be tailored for specific interventions and patient groups. If possible, it would be worthwhile if researchers could establish if observed harms are related to the treatment or not, and differentiate between harms linked to properly delivered treatment and harms due to malpractice.

We would also recommend that researchers report any harmful effects or the absence of such effects, and how harmful effects were measured and monitored. At the least, authors should report if no harm-related data were collected. In line with how standards have been set by several journals for reporting of trials in general [10, 62], the journals could play a key role in improving the reporting of harms by requiring that such information is included. Indeed, journals with high impact may be particularly influential, and it is therefore positive that impact

factor was associated with probability of reporting harms.

Limitations

The results should be viewed in the light of some limitations. First, this review was limited to reports published in one year. While this allowed us to focus on recent trials, it might also limit the generalizability of the results. However, we find it unlikely that the quality of reporting was better before 2010. It therefore seems safe to assume that information about adverse events or deterioration is missing from the major part of the accumulated research within this field. Also, we find it unlikely that the reporting would have changed dramatically since 2010.

Second, although we employed a broad search strategy we might have failed to find a proportion of trials that would otherwise have met the eligibility criteria. There might also be a small number of misclassified reports, although we are confident that we did not miss adequately reported adverse events, side effects or deterioration in the eligible trials. We find it unlikely that the reports we failed to include or any misclassifications would have made substantial changes to the overall pattern of results.

Conclusion

Information about benefits as well as risks needs to be available in order for patients to make an informed choice to engage in psychological treatment. Nonetheless, the risk of harms is very seldom reported within this research field, or only partially reported. We believe that the field of psychological interventions would benefit from more stringent reporting of harms, including clearer definitions and descriptions of the methods used to collect harm-related information.

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Conflict of interest
No conflict of interest reported.

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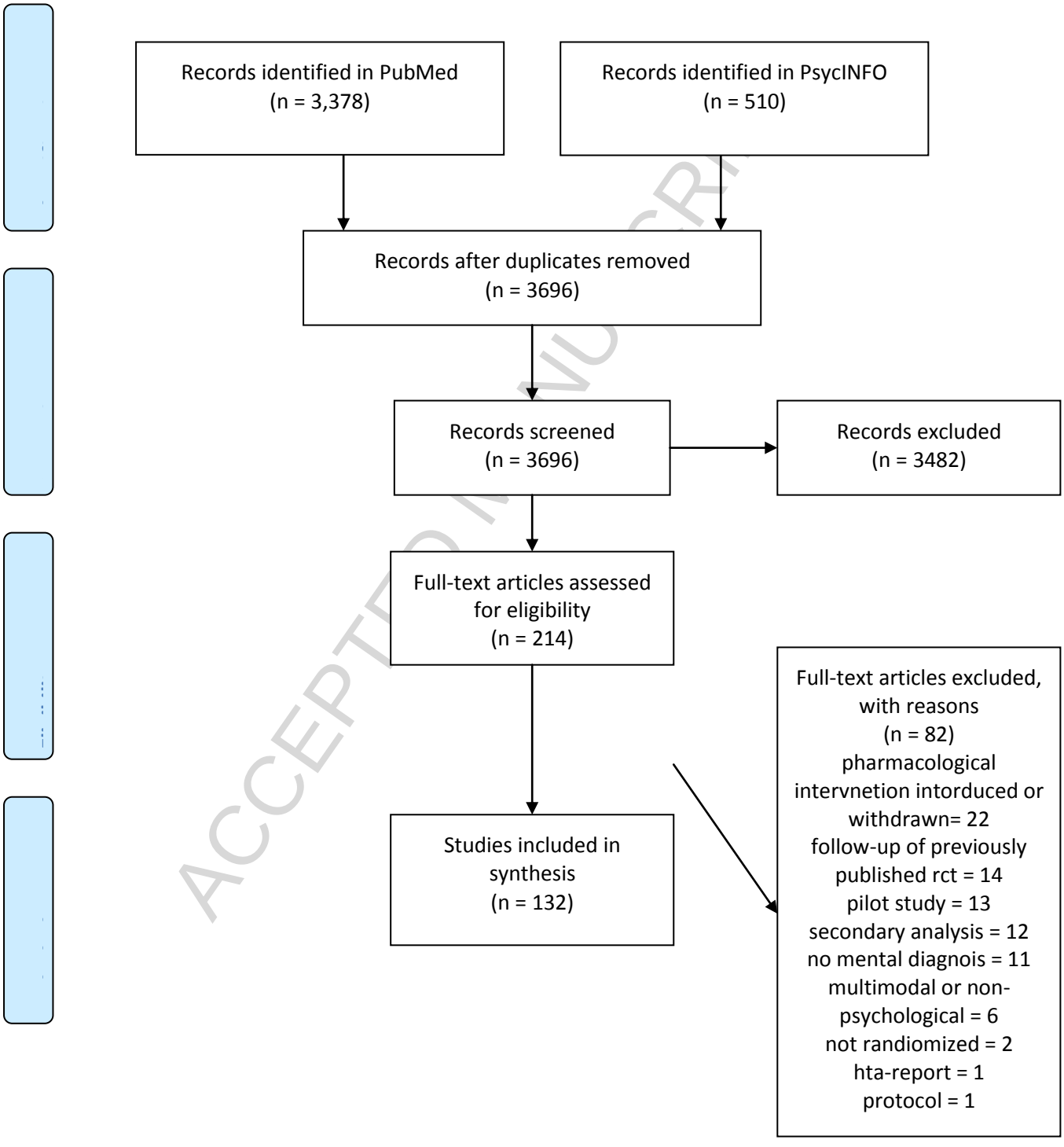

Figure 1. PRISMA flow-chart.

Table 1 Randomized controlled trials of psychological interventions for mental disorders published in 2010 that monitored and reported adverse events, side-effects or deterioration

	Number (%) of trials	
Mental and behavioural disorders (ICD-10)	Total	Information indicating monitoring of adverse events, side-effects or deterioration
Anxiety disorders[a]	31	5 (16%)
Mood disorders	17	3 (18%)
Substance use disorders	14	2 (14%)
Dementias	11	2 (18%)
Reaction to severe stress/adjustment disorders	10	5 (50%)
Eating disorders	9	2 (22%)
Schizophrenia	9	2 (22%)
Pervasive developmental disorders	8	2 (25%)
Specific personality disorders	4	1 (25%)
Other disorders	19	4 (21%)
Any disorder	132	28 (21%)

[a] Including obsessive-compulsive disorder but not post-traumatic stress disorder, which is included in reaction to severe stress/adjustment disorders
ICD-10 = International Statistical Classification of Diseases and Related Health Problems version 10